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Laursen, Sisse Heiden

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BY
SISSE HEIDEN LAURSEN

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Sisse Heiden Laursen

AALBORG UNIVERSITY
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PhD supervisor:	Prof. Ole Kristian Hejlesen, MSc, PhD Aalborg University, Denmark
Assistant PhD supervisor:	Prof. Peter Vestergaard, MD PhD DrMedSc Aalborg University, Denmark
PhD committee:	Associate Professor John Hansen (chairman) Aalborg University
	MD DMSc, James Heaf Sjællands University Hospital
	Professor Ron Summers Loughborough University
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CV

Sisse Heiden Laursen (born in 1983) received her Bachelor's Degree in nursing in 2008 from the University College Nordjylland, Denmark. Afterwards, she worked as a nurse in a dialysis unit at Aalborg University Hospital, Denmark (2008-2012). In 2012, she got her Master's Degree in clinical science and technology from Aalborg University. Subsequently, in 2013, Sisse was enrolled as a PhD student in the doctoral school at the Faculty of Medicine at Aalborg University under the supervision of Professor Ole Kristian Hejlesen and Professor Peter Vestergaard. The thesis was handed in after six and a half years of enrolment, including two years of maternity leave. Over the past two years of the PhD, Sisse has worked simultaneously on other research and teaching activities. During the period from 1 August 2018 to 30 April 2019, she worked full time on a systematic review of the efficacy of telemedicine solutions in patients with diabetes while being employed by the Steno Diabetes Center North Denmark. From 1 February 2019 until now, she has been working full time as a nursing school teacher and researcher at University College Nordjylland.

ENGLISH SUMMARY

Hyperphosphataemia is one of the most common and challenging conditions in haemodialysis (HD) patients, affecting between ~50% and 80% of the patient population. The condition is accompanied by severe complications and premature death. Main interventions in the management of hyperphosphataemia include dietary phosphate restrictions, phosphate-binding agents and dialysis removal. However, the high prevalence of hyperphosphataemia indicates that these approaches are deficient. Current practise is challenged in various ways, for example by the risk of protein malnutrition following dietary restrictions, an insufficient effect of the phosphate-binding agents and ineffective dialytic removal of phosphate due to, for instance, lack of individualised dialysis prescriptions.

Physiological modelling in the form of phosphate kinetic modelling may further our understanding of phosphate kinetics in HD patients. Furthermore, it can help quantify dialytic phosphate removal and has the potential to help individualise current or new treatment regimens and generate new inputs to the teaching part - overall with a view to improving hyperphosphataemia management. This PhD study evaluates current phosphate kinetic modelling approaches in chronic HD therapy and presents new perspectives. The aim is to improve our insight into intra- and post-dialytic phosphate kinetics and to provide novel modelling tools that can aid current practice in hyperphosphataemia management, including perhaps in the handling of dialysis prescribing.

The thesis consists of four studies. The first study is a model study presenting the development and evaluation of a new phosphate kinetic model on average plasma phosphate samples. The model includes a predictive model of intra-dialytic (four- and eight-hour) and post-dialytic (two-hour) values of plasma phosphate in HD therapy. Distribution volume assessment was part of the modelling process. The second study is a systematic review of phosphate kinetic models in HD therapy. The review provides insight into and in-depth comparison of existing models. The review is followed by another model study. Hence, the third study includes modifications and validation of the most promising model variation of the first study, a three-compartment model. The study aims at individualising the model and validating the model on individual patient data with a view to assessing the precision and the temporal robustness of the model predictions. Furthermore, adjustments are made to make the model more consistent with physiological expectations. The fourth and final study is an addition to the model presented in the third study. The focus of this study is to evaluate and validate the addition of an assumed intra-dialytic coagulation component to the model by adding a linear clearance reduction (/h) to the transport component of phosphate between dialysate and plasma.

The results of the thesis indicate that the modelling approaches (Study I, III and IV) seem promising in simulating phosphate kinetics in individual chronic HD patients; especially intra-dialytic phosphate kinetics. The temporal robustness of the model predictions is also cautiously concluded on the basis of Study III. Furthermore, the

idea of adding a coagulation component to the model to simulate intra-dialytic coagulation could provide a promising input to current phosphate kinetic modelling, for instance as a potentially useful tool for detection of clotting problems. Thus, the perspectives and ideas emanating from this PhD study may inform existing knowledge and contribute to devising clinically useful solutions. However, even though promising, the model with and without the coagulation component need further validation, especially with a focus on post-dialytic kinetics. In this regard, it would be highly relevant to test the model on a larger sample and it could be relevant to consider implementing (and validating) other model components that might influence the intra- and post-dialytic plasma phosphate concentration.

DANSK RESUME

Hyperfosfatæmi er en af de mest almindelige og mest udfordrende tilstande hos hæmodialysepatienter (HD-patienter). Tilstanden rammer mellem 50% og 80% af patienterne og er forbundet med alvorlige komplikationer og tidlig død. De overordnede interventioner i håndteringen af hyperfosfatæmi består af diætbegrænsninger, fosfatbindere og dialysefjernelse. Den høje forekomst af hyperfosfatæmi tyder imidlertid på, at disse tilgange er utilstrækkelige. Der findes forskellige udfordringer i den nuværende praksis, herunder risiko for proteinrelateret fejlernæring ved overholdelse af diætbegrænsningerne, utilstrækkelig virkning af fosfatbindere og ineffektiv dialyse bl.a. pga. utilstrækkelig individualisering af dialyseordinationerne.

Fysiologisk modellering i form af fosfatkinetisk modellering er en lovende tilgang til en dybdegående forståelse af fosfatkinetik hos HD-patienter. Desuden kan metoden understøtte beregningerne af den dialytiske fosfatfjernelse samt potentielt understøtte individualisering af nuværende og nye behandlingsregimer samt frembringe nye input til undervisningsdelen - samlet set med henblik på at forbedre håndteringen af hyperfosfatæmi. Dette ph.d.-studie evaluerer aktuelle fosfatkinetiske modeller inden for kronisk HD behandling og præsenterer nye perspektiver på området. Fokus er at højne vores indsigt i forhold til intra- og postdialytisk fosfatkinetik og at levere nye og forbedrede modelleringsværktøjer, der kan understøtte den nuværende praksis i håndteringen af hyperfosfatæmi herunder måske i dialyseordinationer.

Afhandlingen består af fire studier. Det første studie er et modelstudie, der præsenterer udformningen og evalueringen af en ny fosfatkinetisk model med afsæt i gennemsnitlige plasmafosfatprøver. Modellen indbefatter en prædiktiv model af intradialytiske (fire og otte timer) og postdialytiske (to timer) plasmafosfatværdier inden for HD behandling. Det andet studie er et systematisk review af fosfatkinetiske modeller inden for HD, som giver indsigt i og en grundig sammenligning af eksisterende modeller. Reviewet efterfølges af endnu et modelstudie. Det tredje studie omfatter således modifikationer og validering af den mest lovende modelvariation, en trekompartmentmodel, fra det første studie. Dette studie har til formål at individualisere modellen og validere den på individuelle patientdata med henblik på at vurdere præcisionen og den tidsmæssige robusthed af modelprædiktionerne. Formålet er endvidere at justere modellen til at være i bedre overensstemmelse med de fysiologiske forventninger. Det fjerde og sidste studie er en tilføjelse til modellen fra studie tre. Fokus for dette studie er at evaluere tilføjelsen af en intradialytisk koagulationskomponent (kredsløbs- og filterkoagulation) til modellen ved at tilføje det som en lineær clearance-reduktion (/time) til transportkomponenten af fosfat mellem dialysatet og plasma.

Resultaterne af ph.d.-studiet indikerer, at modelleringen (Studie I, III og IV) er lovende i forhold til at simulere fosfatkinetik hos individuelle kroniske HD-patienter især intradialytisk fosfatkinetik. Det kan også med baggrund i Studie III med

forsigtighed udledes, at modelprædiktionerne har en tidsmæssig robusthed. Desuden kan forslaget om at tilføje en koagulationskomponent til modellen med henblik på at simulere intradialytisk koagulation være et lovende input til den nuværende fosfatkinetiske modellering, fx som et potentielt brugbart værktøj til at detektere klotningsproblemer. Perspektiver og ideer fra dette ph.d.-studie kan således muligvis præge den eksisterende viden og dermed måske bidrage til at udvikle nye klinisk nyttige løsninger. Men trods de lovende resultater er der behov for yderligere validering af modellen både med og uden koagulationskomponenten, især med fokus på postdialytisk kinetik. I den forbindelse ville det være yderst relevant at teste modellen på en større population, og det kunne være relevant at overveje at implementere (og validere) andre modelkomponenter med potentiel indflydelse på den intra- og postdialytiske plasmafosfatkoncentration.

PREFACE

The idea for this thesis originates partly from my work as a dialysis nurse in clinical practice and partly from my final semester at the Master's education in Clinical Science and Technology at Aalborg University. In our Master's thesis, my co-student Amanda Buus and I started working with the subject of phosphate modelling in haemodialysis (HD) and obtained promising results. This work inspired me to continue research within the field.

One goal of the present PhD was to survey and compare existing phosphate kinetic modelling approaches in the field of chronic HD therapy. Another goal was to present and evaluate new model solutions in the field in order to devise useful tools for management of hyperphosphataemia in HD patients. Thus, the thesis presents no final solution but offers novel perspectives and ideas that may inform existing knowledge and hence contribute to devising clinically useful solutions.

The thesis was conducted at the Department of Health Science and Technology at Aalborg University, Denmark, from November 2013 to August 2020, with financial support from the Doctoral School in Medicine, Biomedical Science and Technology, Aalborg University, and the Danish Diabetes Academy supported by the Novo Nordisk Foundation.

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Furthermore, I would like to thank all co-authors for their collaboration and their contributions to the studies and papers; thanks to Lise Boel, Amanda Buus, Morten Hasselstrøm Jensen, Lisbet Brandi and Jeppe Hagstrup Christensen.

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Another group of people who have been important for me during the PhD includes my dear colleagues from the Medical Informatics Research Group. I thank you all for making my time as a PhD student enjoyable and for countless discussions about everything from personal issues to MATLAB and statistics. A special thanks goes to my dear colleagues and friends; Stine Hangaard Casper, Pernille Heyckendorff Secher, Amanda Buus, Clara Schaarup and Thomas Kronborg.

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PUBLICATION LIST

This thesis is based on the following four papers:

I. **Laursen SH**, Buus A, Jensen MH, Vestergaard P, Hejlesen OK. Distribution volume assessment using compartment modelling: phosphate kinetics in hemodialysis therapy. Int J Artif Organs. 2015; 38(11): 580-7 (1).

II. **Laursen SH**, Vestergaard P, Hejlesen OK. Phosphate kinetic models in hemodialysis: A systematic review. Am J Kidney Dis. 2018; 71(1):75-90 (2).

III. **Laursen SH**, Boel L, Brandi L, Christensen JH, Vestergaard P, Hejlesen OK. Evaluation of a phosphate kinetic model in hemodialysis therapy – assessment of temporal robustness of model predictions. Submitted to Nephrol Dial Transplant.

IV. **Laursen SH**, Boel L, Brandi L, Christensen JH, Vestergaard P, Hejlesen OK. Implementation of a coagulation component into a phosphate kinetic model in hemodialysis therapy – a potentially useful tool for quantitative detection of clotting problems. Submitted to Nephrol Dial Transplant.

In addition, contribution has been made to the following papers:

- Buus A, Nyvang L, **Heiden S**[1], Pape-Haugaard L. Quality assurance and effectiveness of the medication process through tablet computers? Stud Health Technol Inform. 2012; 180: 348-52 (3).

- **Heiden S**, Buus AA, Jensen MH, Hejlesen OK. A diet management information and communication system to help chronic kidney patients cope with diet restrictions. Stud Health Technol Inform. 2013; 192: 543-7 (4).

  Presented at MEDINFO 2013, Copenhagen, Denmark.

- Lilholt PH, **Heiden S**, Hejlesen OK. User satisfaction and experience with a telehealth system for the Danish TeleCare North Trial: a think-aloud study. Stud Health Technol Inform. 2014; 205: 900-4 (5).

[1] Heiden S and Laursen SH refer to the same person.

- **Laursen SH**, Buus A, Lisbet Brandi, Vestergaard P, Hejlesen OK. A Decision Support Tool for Healthcare Professionals in the Management of Hyperphosphatemia in Hemodialysis. Stud Health Techol Inform. 2018; 247: 810-4 (6).

  Presented at MIE2018, Gothenburg, Sweden.

- Hangaard S, **Laursen SH**, Udsen FW, Vestergaard P, Hejlesen OK. Telemedicine interventions for the management of diabetes: A systematic review and meta-analysis (7).

  Proceedings of MIE2020, Geneva, Switzerland.

ABBREVIATIONS

ADP:	Adenosine diphosphates
AMP:	Adenosine monophosphates
APD:	Automated peritoneal dialysis
ATP:	Adenosine triphosphate
AV:	Arteriovenous
CAPD:	Continuous ambulatory peritoneal dialysis
CKD:	Chronic kidney disease
CHD:	Conventional haemodialysis
DNA:	Deoxyribonucleic acid
FGF-23:	Fibroblast growth factor-23
GFR:	Glomerular filtration rate
HD:	Haemodialysis
HDF:	Haemodiafiltration
HF:	Haemofiltration
KDIGO:	Kidney Disease Improving Global Outcomes
NHD:	Nocturnal haemodialysis
NOS:	Newcastle-Ottawa Scale
PD:	Peritoneal dialysis
PO^{3-}_4:	Inorganic phosphate
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTH:	Parathyroid hormone
RMSE:	Root mean square error
RNA:	Ribonucleic acid
R^2:	Coefficient of determination

RSS: Residual sum of squares

TBW: Total body water

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CHAPTER 1. INTRODUCTION

Hyperphosphataemia, i.e. plasma phosphate >1.4 mmol/L (8), is one of the most frequently observed electrolyte disturbances in haemodialysis (HD) patients. This disturbance affects between ~50% and 80% of dialysis patients (9–11). It is associated with serious adverse outcomes and imposes a significant burden on both patients and healthcare resources. As a result, hyperphosphataemia is widely recognized as one of the most important clinical targets in the treatment of HD patients (8,9,12,13).

The main interventions in hyperphosphataemia management in HD patients include dietary restrictions, phosphate-binding agents and dialysis removal (13–15). However, the high frequency of hyperphosphataemia indicates that these interventions have largely failed and that improvements are needed.

Physiological modelling, in the form of kinetic modelling, can provide an important tool to increase our understanding about the physiological processes and problems when evaluating phosphate kinetics in HD patients (2,16,17). Hence, a model compatible with phosphate kinetics in HD therapy could be beneficial for improving current treatment regimens.

The potential benefits of physiological modelling are the main focus of this thesis. More precisely, the thesis focuses on intra- and post-dialytic phosphate kinetic modelling in chronic HD therapy. The end of goal is to clarify existing modelling approaches and to add new and useful model suggestions to the area of interest.

The thesis is based on four studies. The first study (1) (Study I) includes a description of the development and validation of a new phosphate kinetic model in HD therapy based on distribution volume assessment; a seemingly overlooked approach. The first study is followed by a systematic review (2) (Study II) of phosphate kinetic models in HD therapy. This study aims to identify and provide in-depth insight into existing phosphate models. The third study (Study III) is an addition to Study I. This study aims at improving the best performing model presented in the first study by fitting it to individual patient data aiming at making it more compatible with individual phosphate kinetics and physiological expectations. Furthermore, the study aims to test the temporal robustness of model predictions. Finally, the focus of the fourth study (6) (Study IV) is to add intra-dialytic circuit and dialyzer coagulation as a component to the model variation presented in Study III; an untested approach within phosphate kinetic modelling.

CHAPTER 2. BACKGROUND

This chapter introduces the background for the thesis. It gives a general introduction to hyperphosphataemia in relation to HD. The chapter also describes current interventions in hyperphosphataemia management and offers perspectives on current challenges. This leads to a section that presents the method of physiological modelling, model validation considerations and current challenges in phosphate kinetic modelling in relation to HD therapy.

2.1. HYPERPHOSPHATAEMIA IN HAEMODIALYSIS PATIENTS

The number of people undergoing dialysis continues to increase worldwide. For instance, due to the improved treatment regimens for diabetes and hypertension, the prevalence of dialysis patients is expected to double from approximately 2.62 million worldwide (in 2010) by 2030 (18,19) (14,15). HD therapy is the most common type of dialysis accounting for approximately 89% of dialysis patients (20). Dialysis (or a kidney transplant) becomes necessary when the kidneys fail to uphold vital functions, i.e. when the patient is at the stage of kidney failure. According to international guidelines, the Kidney Disease Improving Global Outcomes (KDIGO), kidney failure is defined as a glomerular filtration rate (GFR) below 15 ml/min/1.73m^2 (14) (Table 1). The GFR, a marker of the stage of kidney disease, denotes the filtration capacity of the kidneys, i.e. the rate at which the glomeruli filter wastes and fluid from the blood each minute (14,15,21,22).

Stage	Specification	GFR (ml/min/1.73 m^2)
G1	Normal or high	≥ 90
G2	Mild decrease	60-89
G3a	Mild to moderate decrease	45-59
G3b	Moderate to severe decrease	30-44
G4	Severe decrease	15-29
G5	Kidney failure	< 15

Table 1. The KDIGO stages of kidney disease (14). GFR: glomerular filtration rate.

Kidney failure is associated with various abnormalities and disorders (14). Hyperphosphataemia is one of the most frequently observed disorders in HD patients caused mainly by the reduced excretion resulting from the impaired renal function (14,15,22,23). The disorder affects approximately 50-80% of the HD population (9–11).

The following subsections give an account of aspects relevant when considering hyperphosphataemia in HD patients.

2.1.1. PHOSPHATE

Phosphorus is a mineral widely present in the human body as inorganic phosphate (PO^{3-}_4). Inorganic phosphate plays an essential role in physiological processes, for instance, bone metabolism, energy metabolism, cellular signalling and glycolysis. Hence, it is most commonly found in phospholipids, nucleotides, deoxyribonucleic acid **(**DNA), ribonucleic acid (RNA) and in forms of adenosine phosphates: monophosphates (AMP), diphosphates (ADP) and triphosphates (ATP) (13,24–26).

The total phosphate content in the adult body is approximately 700 g. About 80%–85% is found in the skeleton as the structural material of bone and teeth where phosphate acts as a buffer to maintain a relatively stable phosphate balance. The remaining 15%–20% is present in body fluids and soft tissues. The extracellular space accounts for 1% of the total body phosphate, mainly as organic phosphate contained in phospholipids. Hence, the amount of phosphate measurable in clinical practice represents <1% of total body phosphate (13,24–26).

Figure 1 provides a simplified overview of the most important physiological mechanisms involved in phosphate regulation in the human body.

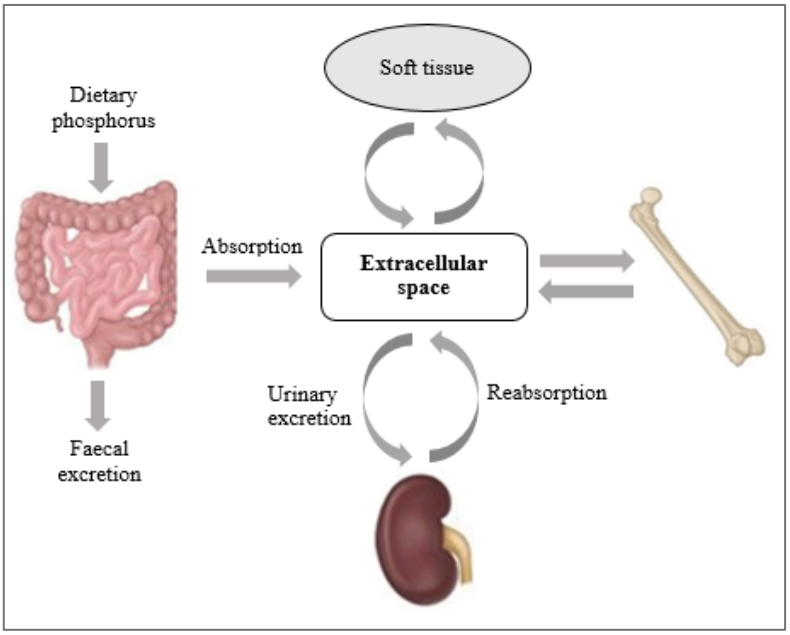

Figure 1. Regulation mechanisms of phosphate in the human body.

2.1.2. BONE AND MINERAL METABOLISM

An introduction to bone and mineral metabolism is a prerequisite to understanding the pathology of hyperphosphataemia and the phosphate balance. This section presents some of the most important elements of the metabolic processes.

Bone and mineral metabolism is a closely regulated process essential for normal growth and a functioning organism. The process is influenced by a number of hormones that establish the phosphate and calcium balance. Some of the most important hormones include calcitriol (active vitamin D), calcitonin and parathyroid hormone (PTH). Calcitonin is secreted from the parathyroid glands, whereas PTH is secreted from the thyroid gland. These hormones primarily act on three organs: kidneys, bones and intestines (26–28).

Phosphate (in the form of phosphorus) and calcium are absorbed through passive and active intestinal processes. The active processes are stimulated by calcitriol which increases intestinal absorption. Calcitriol also contributes to absorption of calcium and renal phosphate secretion. Moreover, calcitriol stimulates the bone calcification processes and the activity of the bone-regulating cells; osteoclasts and osteoblasts (26,27).

PTH has considerable influence on the metabolic processes, all of which serve to regulate blood calcium. Thus, PTH stimulates calcium release and skeletal phosphate resorption, increases renal and intestinal calcium absorption, increases urinary excretion of phosphate and promotes renal conversion of vitamin D to calcitriol. PTH secretion diminishes when there is too much calcium in the blood (negative feedback) but increases in response to low serum calcium or high serum phosphate (positive feedback). Calcitonin helps remove calcium from the blood at high serum concentrations (positive feedback) by inserting it into the bones and by increasing renal excretion (26–28).

Table 2 outlines the involvement of organs and hormones in bone and mineral metabolism. The metabolic processes are also influenced by the hormone fibroblast growth factor-23 (FGF-23), the main function of which seems to be regulation of plasma phosphate. The hormone is secreted by osteocytes and osteoblasts in response to elevated plasma phosphate and calcitriol and decreases renal phosphate reabsorption and increases urinary excretion. FGF-23 may also suppress the enzyme 1-alpha-hydroxylase reduce and thereby reduce vitamin D activation (26,29–33).

Hormone	**PTH** 	**Calcitriol** 	**Calcitonin** 
Factors stimulating production	↓ plasma calcium ↑ plasma phosphate	↑ PTH ↓ plasma calcium ↓ plasma phosphate	↑ plasma calcium
Factors inhibiting production	↑ plasma calcium	↓ PTH ↑ plasma calcium ↑ plasma phosphate	↓ plasma calcium
 **Intestines**	↑ absorption of calcium	↑ absorption of calcium and phosphate	↓ calcium absorption
 **Kidneys**	- ↑conversion of vitamin D to calcitriol - ↑ reabsorption of calcium - ↑ excretion of phosphate	↑ reabsorption of calcium ↑ secretion of phosphate	↓ reabsorption of calcium
 **Bones**	Stimulates release of calcium and resorption of phosphate from skeleton	Stimulates calcification processes and osteoclast and osteoblast activity	Furthers calcium uptake in bones
Net effect on blood concentrations of calcium and phosphate	↑ calcium ↓ phosphate	↑ calcium ↑ phosphate	↓ calcium

Table 2. Overview of the hormonal involvement in bone and mineral metabolism. PTH: Parathyroid hormone.

2.1.3. HYPERPHOSPHATAEMIA-RELATED CONSEQUENCES

Declining kidney function will eventually lead to disturbances in bone and mineral homeostasis. These disturbances include 1) altered blood levels of phosphate, calcium, PTH and calcitriol, 2) extra-skeletal calcifications and 3) disturbances in bone modelling or remodelling (26,34).

Hyperphosphataemia is observed when GFR reaches approximately 20-35 ml/min/1.73 m^2 (see Table 1) (14,21,26). The disturbance accelerates the progression of kidney disease and results in changes in bone and mineral metabolism, which has different physiological consequences (14,15,32,34,35). The changes and some of the related consequences of hyperphosphataemia are outlined in Figure 2.

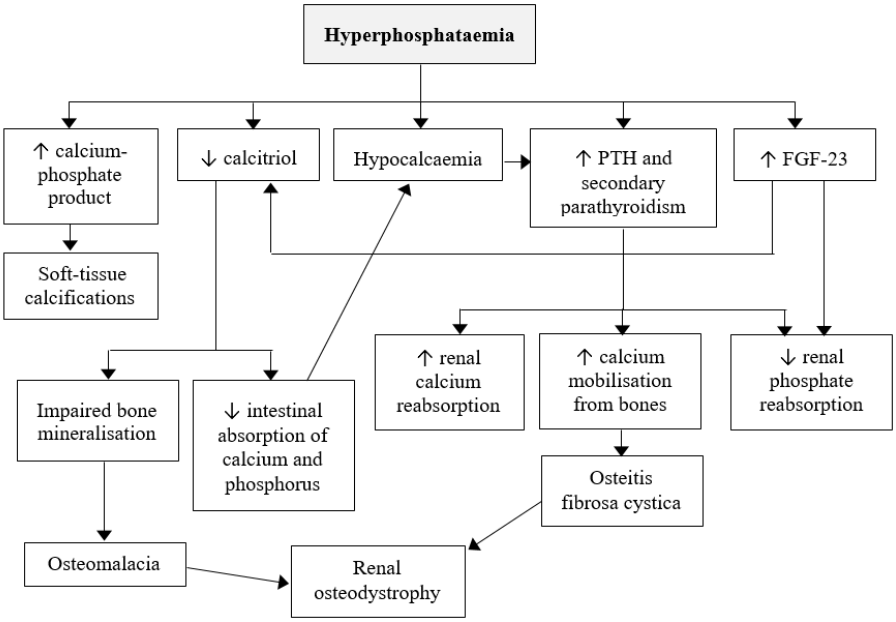

Figure 2. Changes relating to hyperphosphataemia and some of the related consequences. PTH: Parathyroid hormone; FGF-23: Fibroblast growth factor-23.

Hyperphosphataemia is known to accelerate vascular calcifications processes. This is mainly due to an increase in the calcium-phosphate product (see Figure 2) as a result of the direct increase in phosphate and the reduced mobilisation of minerals in bones. If the calcium-phosphate product is too high, it crystallises and is deposited within the vasculatures and soft tissues (26,34,36). Hence, it is recommended that the calcium-phosphate product does not exceed 55 mg^2/dL^2 (37). Vascular calcifications occur even in younger patients and are common in HD patients. For instance, coronary artery calcifications are observed in 70-80% of HD patients (26).

Vascular calcifications are highly associated with cardiovascular events (12,26,38,39). The risk of cardiovascular events increases exponentially with decreasing kidney function; a process that begins already when the kidney function is reduced by one third (39).

Cardiovascular complications increase the risk of death even in younger HD patients and contribute to approximately 50% of all deaths among HD patients (40,41). For instance, the risk of cardiovascular mortality is approximately 10-30 times higher in HD patients than in the general population (42,43). The correlation between an increase in plasma phosphate and premature death in chronic kidney disease (CKD) patients was presented in 2011 in an extensive systematic review and meta-analysis. The review found that the overall risk of death rose by 18% for each 0.3299 mmol/l increase in plasma phosphate (44).

Secondary and tertiary hyperparathyroidism are other consequences of hyperphosphataemia that cause excessive PTH secretion. As illustrated in Figure 2, it is evident that hyperparathyroidism can be a result of the direct or indirect influence of high plasma phosphate levels. An indirect mechanism includes a decrease in serum-free calcium as hypocalcaemia stimulates PTH secretion. Moreover, hyperphosphataemia leads to hyperparathyroidism because of decreased renal calcitriol production, either directly or indirectly by increasing FGF-23 levels. Symptoms of hyperparathyroidism include bone and joint pain, fragile bones, limb deformities, kidney stones, excessive urination, abdominal pain, nausea, vomiting, loss of appetite, weakness, fatigue, depression, forgetfulness and immune system effects (21,45,46).

Another consequence of hyperphosphataemia that affects most HD patients is renal osteodystrophy (47). Renal osteodystrophy is a bone disease occurring when the kidneys fail to sustain proper blood levels of phosphate and calcium. As illustrated in Figure 2, this may be due to an increase in PTH or a decrease in renal calcitriol production. Renal osteodystrophy includes a number of underlying bone diseases such as osteoporosis, adynamic bone disorder, osteomalacia and osteitis fibrosa (see Figure 2). The condition contributes to bone fractures, bone pain, myopathy, muscle pain, tendon ruptures and periarthritis. For instance, the incidence of hip fracture has been found to be more than five times higher in HD patients than in the average population (48).

The severe consequences of hyperphosphataemia impose a significant burden on both patients and healthcare resources. Therefore, control of this marker is crucial.

2.2. MANAGEMENT OF HYPERPHOSPHATAEMIA

The overall aim of hyperphosphataemia management in HD patients is to maintain plasma phosphate at a near-normal range of 0.9–1.4 mmol/l (8,9). Hyperphosphataemia prevention and treatment include a combination of dietary phosphate restrictions, administration of phosphate-binding agents to reduce intestinal phosphorus absorption, calcitriol supplementation and adequate dialysis removal (14,15). Hyperphosphataemia treatment is relevant when GFR reaches approximately 20-35 ml/min/1.73 m^2 (14,21). At this point, dietary modifications and phosphate-binding agents are usually enough to achieve phosphate levels within the normal range. In the end-stage of the disease (GFR< 10 ml/min/1.73 m^2), dialysis (or transplantation) becomes necessary to maintain a normal phosphate balance (14).

This section presents the monitoring guidelines and procedures for managing hyperphosphataemia in HD and elaborates on the three main interventions: dietary restrictions, treatment with phosphate-binding agents and dialysis. The final section in this part addresses challenges encountered in current practice.

2.2.1. MONITORING HYPERHOSPHATAEMIA

Regular blood samples are obtained according to international guidelines (15) to detect abnormal plasma phosphate values and support regulation of phosphate through dietary measures and doctor's prescriptions. The frequency of blood phosphate sampling in HD is typically once a month, but the monitoring interval is between one and three months.

Blood sampling results support the patient's diet and phosphate binder intake and healthcare professionals' recommendations and doctor's prescriptions (15).

2.2.2. DIETARY RESTRICTIONS AND PHOSPHATE-BINDING AGENTS

A phosphorus-lowering diet, i.e. food items low in phosphate, is the first step in preventing and managing reduced phosphate secretion. This includes a recommended phosphorus intake of 800-1000 mg/day (14,15). The average phosphorus intake in healthy adults is approximately 1000-1400 mg/day (26). The dietary restrictions include reduced intake of dairy products, meats, fish, whole grain products and other food items high in phosphorus. Moreover, home-made meals are recommended because of a high phosphorus content in various food additives (26,49,50). Normally, the intestinal absorption of phosphorus is about 60-70% (26). However, the intestinal absorption of phosphorus is about 80% in patients treated with calcitriol (13,51). Calcitriol accounts for most of the uptake in HD patients as the ability to activate vitamin D is reduced when kidney function declines (14,15).

Usually, dietary restriction is supplemented with phosphate-binding agents when GFR<25-35 ml/min/1.73m^2 (see Table 1)(14,15). Hence, at this point, up to 88% of CKD patients already need phosphate-binding agents to ensure a normal phosphate balance (52). Phosphate-binding agents reduce gastrointestinal absorption of phosphorus when it is consumed before, during or immediately after a meal. They reduce the absorption by forming poorly soluble compounds with phosphorus in the intestinal tract and by ensuring excretion of phosphorus (53).

2.2.3. HAEMODIALYSIS

HD is a procedure that substitutes many of the normal kidney functions by removing excess water, solutes and toxins from the blood using a special dialysis solution, dialysate. In HD, blood is circulating in a closed extracorporeal system and through an external filter (a dialyzer) that contains a semipermeable membrane that helps remove waste and water mainly by diffusion to the dialysate. The blood is accessed using either an arteriovenous (AV) fistula, a central venous catheter or an AV graft (54,55). Other treatment modalities include some HD subtypes; haemofiltration (HF) and haemodiafiltration (HDF). HF is a convective technique that does not include dialysate. Instead, it uses a large amount of ultrafiltration to remove the waste products. The removed fluid is exchanged with sterile replacement fluid. HDF is a treatment modality where HD and HF are performed simultaneously (54,55). Table 3 shows some examples of the ranges of phosphate removal by different treatment modalities (13).

Treatment	Grams per week
CHD, 4 hours	2.3-2.6
Extended HD, ≥ 5 hours	3.0-3.6
NHD, ~ 8 hours	4.5-4.9

Table 3. Ranges of phosphate removal by different dialysis modalities (13). CHD: Conventional haemodialysis; NHD: Nocturnal haemodialysis.

2.2.4. CHALLENGES IN CURRENT PRACTICE

Normalisation of plasma phosphate is difficult to obtain in HD patients (56). One challenge is non-adherence to the recommended dietary restrictions (56,57). An extensive systematic review of dietary adherence in end-stage kidney disease (72% HD studies) reports non-adherence in 43.5–84.5% of patients (58). This is supported by another study reporting that 75-85% of HD patients do not adhere to overall CKD dietary restrictions that include sodium, phosphorus, potassium and fluid intake (57). Moreover, it is estimated that food additives account for 10–50% of total phosphorus intake per day, an aspect which complicates adherence to dietary recommendations (49). As phosphorus is naturally found in protein-rich foods such as dairy products, meat and fish, adherence to dietary restrictions is further complicated by the risk of protein malnutrition. This problem needs to be addressed as protein malnutrition is associated with an increased risk of morbidity and mortality (59). Dialysis patients are at particular risk of protein malnutrition due to, for instance, loss of appetite, chronic inflammation and dialysis-associated amino acid and protein loss. Thus, it is estimated that approximately 20-50% of dialysis patients suffer from protein malnutrition (59). Because of the high risk of malnutrition in particular, dietary phosphate restriction is not sufficient to control plasma phosphate levels (13).

Another challenge in the management of hyperphosphataemia includes insufficient phosphate binder intake. Hence, most patients receiving phosphate-binding agents do not achieve target phosphate levels (60). A systematic review from 2015 of 44 studies on medication adherence in HD patients found that 13-99% (median 53%) did not adhere to phosphate binder regimens (61). One reported issue is non-adherence due to forgetfulness, indifference, lack of understanding, total pill burden and depressive symptoms (61–63). Another issue is the prescription of a standard phosphate binder regimen, typically 2-3 tablets three times a day, which does not allow for variations in meal content. This introduces a problem as phosphate intake typically varies between 100 and 800 mg during the day. Hence, studies indicate that only 30% of meals include an adequate phosphate binder dosage (24,64). In addition, snacks tend to be ignored even though snacks are found to contribute to up to 400 mg of the total daily phosphate intake (64). A third issue relating to phosphate-binding agents includes various side effects such as gastrointestinal disturbances, aluminium toxicity and calcium overload (24,65). Finally, phosphate binder prescriptions are restricted due to economic considerations (62).

Dialysis treatment is also associated with different challenges in the management of hyperphosphataemia. One challenge is that phosphate tends to bind firmly to water

particles in the blood which hinders diffusion of phosphate to the dialysate (66). Moreover, there seems to be an intra- and inter-dialytic inflow of phosphate into plasma from other body compartments. For instance, it is well-studied that the blood phosphate level drops rapidly during the 2 hours of conventional 4-hour HD (CHD) treatment and then stabilise. This is followed by a rebound of plasma phosphate beginning either at the end of treatment or after dialysis is terminated (51,67–69). However, in spite of these known challenges, dialysis treatment is known to contribute to a better phosphate balance by increasing the dialysis frequency or duration (13,15,70). For instance, a systematic review of extended nocturnal HD (NHD) compared with CHD showed a decrease in serum phosphate levels of 0.97 mg/dL in an 8-hour NHD dialysis session compared with a 4-hour CHD treatment (71). However, convincing patients to stay longer on dialysis may be difficult if they are not undergoing treatment at home as they already spend many hours in the dialysis ward. Another problem is that many patients miss treatments or shorten the treatment time. For instance, a review on phosphate-control adherence has reported that 32% of HD patients shorten their treatment time, whereas up to 35% miss treatments occasionally (56).

It should also be emphasised that different dialysis parameters such as dialyzer as well as blood and dialysate flow rates may influence dialytic phosphate removal. Moreover, it has been found that phosphate clearance decreases with increasing haematocrit and coagulation of the extracorporeal system and dialyzer (69,72,73).

Another relevant challenge that needs to be addressed is an observed lack of insight among HD patients into key aspects of their treatment and disease. Different studies point out that this may be related to insufficient information (74,75). An important area where there appears to be inadequate information is within diet and medicine (59,76–78). This poses a significant problem, as sufficient information on dietary regimes and related drug intake appears to be a key need among patients (78). It is apparent in this context that sufficient information and guidance have a positive effect on the individual's independence and adherence to treatment recommendations. Insufficient information and lack of insight may thus lead to an increased risk of disempowering the patient and unsatisfactory compliance with dietary and phosphate binder restrictions (78,79).

2.3. PHOSPHATE KINETIC MODELLING IN HAEMODIALYSIS

The high frequency of hyperphosphataemia in HD patients indicates that current practice is insufficient and deserves attention (9,10). To make changes to current practise, it is important to have an in-depth understanding about the phosphate kinetics of the population of concern. Physiological modelling in the form of kinetic modelling is widely used and can provide new insights furthering our understanding and handling of biological processes, for instance by investigating new dialysis methods (16,80). Other practical applications could take the form of model-based decision support. Hence, model-based decision support could perhaps help individualize current HD treatment regimens and work as an integrated decision support tool, for instance as part of dialysis adjustments, or it could serve educational purposes with a

view to improving hyperphosphataemia management. Altogether, practical approaches would have to be working well, and a phosphate kinetic model would have to be accurate to ensure that the tool is reliable (16,17,80).

This section presents the methods of physiological modelling and model validation and sheds light on current challenges related to phosphate kinetic modelling in HD therapy.

2.3.1. PHYSIOLOGICAL MODELLING

Physiological modelling is a representation of physiological reality expressed in the form of mathematical equations. The modelling approach aims to characterise the interactions of physiological subsystems, including various processes such as absorption, distribution and elimination in the body. These subsystems include one or more interconnected body compartments consisting of organs, body fluids and/or tissue spaces, etc. Moreover, the modelling approach considers observed physiological variables such as flow rates of circulating body fluids, body composition and the function of involved organs and plasma. Physiological modelling is a useful approach in various applications in biomedical engineering and medicine, especially in drug research and development (16,17). It is also applied within HD in the form of urea and creatinine modelling to predict the effect of dialysis techniques and procedures and to analyse the course of treatment, etc. Hence, physiological modelling can help the physician tailor treatment to the individual patient (16,54,81,82).

The simplest physiological model is one that comprises a single compartment. This is often referred to as a one-compartment model that is normally set equal to the systemic blood circulation because it can be measured. The compartment includes a set of model equations for the mass, concentration and distribution volume for the given drug or substance of interest. Model equations are influenced by a number of parameters or variables, *inputs*, and generate some estimates or predictions of physiological variables - referred to as *outputs* (16,17). This specific model approach is illustrated in Figure 3.

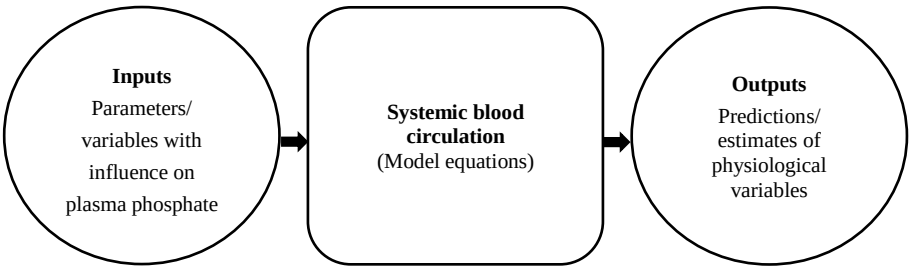

Figure 3. Example of one-compartment model equal to systematic blood circulation.

Depending on their purpose, physiological models are typically divided into four

categories; predictive, descriptive, interpretive or explanatory. *Predictive models* can help determine how a system would react to changes or stimuli and thereby forecast future outcomes; for instance, they could be used to simulate how plasma phosphate would respond to dialysis treatment or dietary intake. *Descriptive models* are applied to describe quantitative relationships or systems accurately and briefly by mathematical expressions; for instance, they could describe a linear equation of two proportional variables. This approach would be simpler than a verbal or graphical description. The *interpretive models* are typically used to interpret experimental results; for instance, an interpretive model of renal function could include simulations of creatinine, and urea could be applied to forecast a recommended time for the next HD treatment for the individual patient. Finally, *explanatory models* can help explain some physiological changes, processes and effects in a system. Moreover, physiological models can be applied to estimate different parameters that are difficult to determine based on the available variables like input, for instance by using explanatory models (16,17).

2.3.2. MODEL VALIDATION

Thorough model validation and uncertainty assessment on the basis of experimental data are critical to ensure reliable model results. This should be an ongoing activity both during the development phase and once the model is complete. If the model is assessed to be in good agreement with the experimental data, it could be used as a tool for gaining insight into biological systems and to identify gaps in knowledge about the systems. If it is a predictive model, it could enable prediction of the future course of the biological system or variable (16,17). Hence, developing a reliable phosphate kinetic model could be an ideal approach for increasing our understanding of the complexity of phosphate kinetics in HD patients. A good predictive phosphate model could also forecast the course of plasma phosphate in different dialysis regimens and with the use of different parameters and thereby inform appropriate dialysis prescriptions tailored to the individual patient.

A valid model is a model that successfully passes through the validation process. Thus, physiological modelling requires model validation as an ongoing process beginning when specifying the purpose of the modelling activity and ending when the model is complete. If new relevant theories and data become available, it could be necessary to make further adjustments to the model. Such modifications would involve further validation of the model (16,17).

Cobelli et al. (2019) define model validation as follows:

> *"Model validation involves assessing the extent to which a model is well-founded and tractable, while fulfilling the purpose for which it was formulated"* (16).

According to this definition, the validation approach first of all requires a clear and precise purpose. Hence, model validation involves evaluating the worth of the model to its intended purpose. If the purpose is not clearly stated, it will be impossible to

make the necessary judgment as to whether the specific model is appropriate for its purpose or not (16). As implied in the definition, model validation is about evaluating whether the model is well-founded and tractable. To be well-founded, it is essential that the approach is thoroughly argued and that valid assumptions are made on the basis of relevant chemical and physical laws and principles that are being represented. To be tractable, the model has to be easily accessible and manageable in satisfying its intended purpose (16,17).

According to Cobelli et al., the model will need to satisfy one or more of four criteria to be considered valid. The four criteria include theoretical, empirical, pragmatic and heuristic validity. The four validity criteria are outlined in Table 4.

Validity criteria	Assessment approach/focus
Theoretical validity	Is the assessment of the extent to which the model is compatible with accepted physiological theories → Is the model theoretically valid?
Empirical validity	Is the assessment of how well the model fits available empirical data → Is the model empirically valid?
Pragmatic validity	Is the assessment of the degree to which the predictive models support clinical decision making. The focus is to assess whether the model works with sufficient accuracy for the predictions to be clinically useful → Is the model pragmatically valid?
Heuristic validity	Is the assessment of the extent to which the model can be used to test physiological hypotheses → Is the model heuristically valid?

Table 4. The four validity criteria in model validation according to Cobelli et al. (16).

Which of the four validity criteria would be relevant in the particular case is, of course, problem-specific and dependents on the intended purpose of the modelling activity (16). When the model′s validity is evaluated on the basis of experimental data, it is essential to consider the quality of these data. Thus, a successful outcome of the modeling activity will not only depend on the quality of the model. It will also critically dependent on the quality of the experimental data used to assess the model (16,17). High-quality experimental data require a rather controlled research process and setting to minimise bias, confounding, etc. Moreover, a suitable sample size is important to ensure an adequate data collection (83). Model validation on the basis of experimental data typically involves statistical and graphical comparisons; for instance, calculation of the coefficient of determination (R^2) and the root-mean-square error (RMSE) (16,17).

The validation process when comparing competing candidate models is another relevant perspective in the area of model validation. This process involves determining which of the models performs best in relation to the intended purpose; for instance, by comparison of RMSE or R^2 values (16).

2.3.3. CHALLENGES AND LIMITATION RELATED TO PHOSPHATE KINETIC MODELLING

Phosphate kinetic models in HD therapy are available, but no model seems to have gained clinical acceptance, maybe because of the high complexity of phosphate kinetics which challenges the development and evaluation of phosphate kinetic models (54,81). Hence, even though various physiological and treatment-related components could influence the phosphate level (64,84–87), most existing models seem rather simple and incorporate only few model parameters. For instance, four identified models (88–91) only include between two and four relevant model components, e.g. dialyzer phosphate clearance and total distribution volume; and they ignore other known influencing parameters such as ultrafiltration rate, blood flow rate, coagulation of the dialyzer (and extracorporeal system) and haematocrit (64,72,73,84–87). Thus, one could question the theoretical validity of the models; and, indeed, if it is relevant at all to judge if the models have high empirical (and pragmatic) validity (16). Another perspective which also potentially hinders the development and evaluation of phosphate models is the lack of research into how phosphate models could be applied in practical settings. Hence, with no clear field of application, the motivation for and relevance of phosphate modelling presumably decreases.

So far, mainly two-compartment models and pseudo-one compartment models, i.e. models with an accessible compartment plus an unknown contributor, have been proposed (88,89,92–94). However, these models are limited in different ways, for instance, due to unclear validation results, paediatric therapy and intra-dialytic HD exclusively. Hence, the potential for a new and improved model study seems obvious. In this regard, it could be relevant to investigate to which extent a multi-compartment model with more than two compartments could be beneficial in simulating phosphate kinetics in HD therapy. A four-compartment model was presented in 2002 by Spalding et al. (68) showing promising results. However, this model seems rather complex if it has to work in a clinical setting, and it only accounts for one hour post-dialytic phosphate kinetics.

Another unexplored area is to thoroughly compare existing phosphate kinetic models in HD therapy. The absence of such a comparison calls for a systematic review in this particular modelling field. A comprehensive survey and comparison of available phosphate models in terms of their applicability, contents and clinical feasibility would inform to the current debate about their potential and limitations, for example in relation to components, assumptions and clinical applicability. Hence, such a comparison could further clinicians and researchers' insights and thus inspire further model development and validation.

2.4. BACKGROUND SUMMARY

Hyperphosphataemia is frequently observed in HD patients, and it is associated with serious adverse outcomes such as secondary and tertiary hyperparathyroidism, renal osteodystrophy, vascular calcifications and premature death. The phosphate balance

is regulated by complex processes as part of the bone and mineral metabolism, which includes various hormones and organs.

The main interventions in the management and prevention of hyperphosphataemia include dietary restrictions, phosphate-binding agents and dialysis removal (HD or PD). However, the high prevalence of hyperphosphataemia indicates that current interventions have failed substantially and that current practice needs improvements. There seems to be no simple and unambiguous answer to this problem. Dietary restrictions solve some of the problems, but the restrictions are not always respected due to, for instance, the risk of protein malnutrition. This problem also applies to conventional phosphate-binding agents which are neither consistently reliable nor sufficiently effective; and, moreover, they have a range of side effects. In comparison, prolonged dialysis could represent an effective solution. Hence, frequent and long-term HD treatment is known to have a positive effect on the phosphate balance. However, dialysis phosphate kinetics are complex and not fully understood, and it is questionable if patients would choose an extended treatment regimen.

Physiological modelling could be used for improving the management of hyperphosphataemia in HD patients. For instance, a duly functioning and validated model could help improve our understanding of the complexity of phosphate kinetics and thus potentially help individualise HD treatment to enhance dialytic phosphate removal. Furthermore, such a model could maybe also be used for educational purposes. However, no phosphate kinetic models have yet gained clinical acceptance. A particularly cumbersome issue in this context is the high complexity of phosphate kinetics, which challenges the development and evaluation of phosphate kinetic models. Moreover, it seems like existing models and modelling studies are limited in different ways. Examples are unclear validation results, paediatric focus, questionable practical use and insufficient post-dialytic considerations. Also, current models except for one include only up to two compartments. These aspects and limitations call for new model studies. A systematic review of existing phosphate models would also be highly relevant as no review includes a comparison and survey of existing phosphate kinetic models in HD therapy.

CHAPTER 3. THESIS OBJECTIVES

The previous chapters described how hyperphosphataemia is one of the most important and challenging clinical targets in the treatment of HD patients. If left untreated, hyperphosphataemia significantly increases the risk of morbidity and mortality. Hence, devising appropriate methods for managing and optimising HD patients' phosphate balance is crucial, especially since no sustainable solution has yet been found with which to achieve stabilised phosphate levels in HD patients. Dialysis regulation and individualisation are possible solutions to obtain better phosphate control. Devising such solutions requires profound insight in and in-depth understanding of intra- and post-dialytic phosphate kinetics together with relevant decision support tools to assist optimal dialysis prescriptions. Phosphate kinetics modelling is seen as a potential tool in this regard and constitutes the focal point of this thesis.

The overall research hypothesis of the thesis is that a three-compartment model can accurately simulate phosphate kinetics in haemodialysis.

The overall objective of the thesis is two-fold;

1) On the one hand, this thesis seeks to introduce novel model approaches as existing phosphate kinetic models in the field of HD seem to be inoperative or insufficient in different ways. Therefore, one objective is **to present a novel model with the ability to simulate and predict intra- and post-dialytic phosphate kinetics in HD patients.**

2) On the other hand, as a comprehensive survey and comparison of existing phosphate models is lacking, this thesis also seeks to gain in-depth insight into existing phosphate kinetics models. Therefore, another objective is **to present a systematic review of current models.**

Papers I, III and IV aim to address the first objective, and Paper II aims to address the second objective. Table 5 provides an overview of the connection between the underlying objectives, papers and study approach(es).

The thesis will exclusively focus on hyperphosphataemia management in chronic HD patients and it will not address hyperphosphataemia management related to other dialysis modalities or to the kidney transplant area.

Study	Title of paper	Research objective(s)	Study approach(es)
I	*Distribution volume assessment using compartment modelling: phosphate kinetics in haemodialysis therapy* (1)	To develop and test a new predictive phosphate kinetic model in HD with the aim of using distribution volume assessment to determine distribution volumes values	Compartment modelling and model validation on mean experimental data based on sampling from eight HD patients
II	*Phosphate kinetic models in haemodialysis: A systematic review* (2)	To review the field of phosphate kinetic models to gain further insight into their potential and limitations	Systematic review of existing phosphate kinetics models
III	*Evaluation of a phosphate kinetic model in haemodialysis therapy –assessment of temporal robustness of model predictions*	To improve the best performance model from Study I by individualising the model, making it more compatible with physiological expectations and testing its temporal robustness	Compartment modelling and model validation on individual samples from 12 HD patients collected during two separate treatments per patient
IV	*Implementation of a coagulation component into a phosphate kinetic model in haemodialysis therapy – a potentially useful tool for quantitative detection of clotting problems*	To test if a phosphate kinetics model improves when a linear clearance reduction is added as an assumed intra-dialytic coagulation component	Compartment modelling and model validation using the same patient data as Study III

Table 5. Overview of the studies, papers, research aims and study approach(es).

The following four chapters present some key aspects of each of the four studies that were conducted as part of the PhD thesis.

CHAPTER 4. STUDY I

This chapter summarises the work conducted in the paper entitled "Distribution volume assessment using compartment modelling: phosphate kinetics in hemodialysis therapy" (1)*. The summary focuses on the methods, results and conclusions.*

4.1. METHODS

The first study aimed to develop and test a new model approach of intra- and post-dialytic (2 hours) phosphate kinetics in HD therapy. This section presents the model and evaluation approaches.

4.1.1. PHOSPHATE KINETIC MODEL

The model approach was used to simulate plasma phosphate during HD as a function of time and two hours after treatment. The goal was to achieve the best prediction of plasma phosphate using a simple model comprising predictive compartment modelling with one-, two-, and three-compartment simulations with 15 minutes in between simulations. Diffusive phosphate transport between compartments and a linear model structure were assumed in the two- and three-compartment simulations. Moreover, assumptions were made that three parameters, *f1-f3*, were the only parameters influencing plasma phosphate: f_1 = phosphate eliminated through dialysis clearance at time t, f_2 = diffused phosphate between compartments 1 and 2 at time t, and f_3 = diffused phosphate between compartments 2 and 3 at time t. Figure 4 illustrates the model structures and location of the three parameters *f1-f3*. The phosphate concentration in compartment 1 was consistent with plasma phosphate in all model approaches.

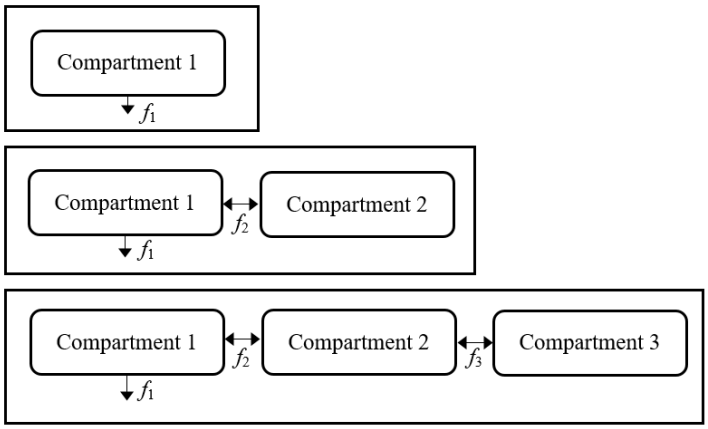

Figure 4. The one-compartment (upper), two-compartment (middle) and three-compartment (bottom) model structures including the location of the parameters f1-f3.

Table 6 provides an overview of all components in the modelling approach, including information on how the individual component was determined.

Com-ponent	Description	Determination of model component
C_1	Phosphate concentration (mmol/l), compartment 1	$C_1(t+1) = \frac{M_1(t)-(f1(t)+f2(t))\times((t+1)-(t))}{V_1}$ (or $\frac{\Delta[PO_4^{3-}]}{\Delta t} = \frac{f1-f2}{V_1}$)
C_2	Phosphate concentration (mmol/l), compartment 2	Two-compartment model: $C_2(t+1)\_a = \frac{M_2(t)+f2(t)\times((t+1)-(t))}{V_2}$ Three-compartment model: $C_2(t+1)\_b = \frac{M_2(t)+(f2(t)-f3(t))\times((t+1)-(t))}{V_2}$
C_3	Phosphate concentration (mmol/l), compartment 3	$C_3(t+1) = \frac{M_3(t)+f2(t)\times((t+1)-(t))}{V_3}$
M_1	Mass of phosphate (mmol), compartment 1	$M_1(t+1) = M_1(t)-(f1(t)+f2(t))\times((t+1)-(t))$
M_2	Mass of phosphate (mmol), compartment 2	Two-compartment model: $M_2(t+1) = M_2(t)+f2(t)\times((t+1)-(t))$ Three-compartment model: $M_2(t+1) = M_2(t)+(f2(t)-f3(t))\times((t+1)-(t))$
M_3	Mass of phosphate (mmol), compartment 3	$M_3(t+1) = M_3(t)+f2(t)\times((t+1)-(t))$
V_1	Volume of distribution (l), compartment 1	Estimated (a man weighing 70 kg): 3 l or 14 l
V_2	Volume of distribution (l), compartment 2	Estimated (a man weighing 70 kg): 3 l, 11 l or 35 l
V_3	Volume of distribution (l), compartment 3	Estimated (a man weighing 70 kg): 8 l or 35 l
f_1	Phosphate eliminated through dialysis clearance (mmol/min)	$f_1(t) = k_d \times (C_1(t)-C_d(t)) \times s$
f_2	Phosphate diffused between compartment 1 and 2 (mmol/min)	$f_2(t) = k_1 \times (C_1(t)-C_2(t))$
f_3	Phosphate diffused between compartment 2 and 3 (mmol/min)	$f_3(t) = k_2 \times (C_2(t)-C_3(t))$
k_d	Dialyser clearance of phosphate (l/min)	Estimated: 1, 1.4, 2, 2.5, 2.8, 3.5, 6 or 9 l/min
k_1	Mass transfer coefficient 1 (l/min)	Estimated: 3, 3.5, 5, 9 l/min
k_2	Mass transfer coefficient 2 (l/min)	Estimated: 1 or 5 l/min
S	Dialysis status	(0 = no, 1= yes)

Table 6. Overview of the model components.

4.1.2. MODEL MODIFICATION AND VALIDATION

The model simulations were modified and tested on experimental data (95), including plasma phosphate samples from eight HD patients undergoing 4-hour and 8-hour HD combined with 2-hour post-dialysis. The samples included the mean values of eight measures obtained during each of the two treatment regimens.

Different steps were applied to modify and test the model simulations and to determine the best model approach:

- Graphical modifications were made to modify and identify the best model simulations in the 4- and 8-hour treatment. This included changing the structure of the model (one, two or three compartments) and its components (V_1, V_2, V_3, k_d, k_1 *and* k_2).
- R^2 calculations of the best graphical results.
- Calculation of mean R^2 values in each pre-selected V case.
- Direct comparison of the means from step 3 between the 4-h and 8-h treatments.
- With each treatment, the best model performance was tested using the opposite treatment regimen (ignoring k_d). This included evaluation and comparison of graphical results and calculation of R^2 values.
- The results of steps 4 and 5 were compared to determine if the two R^2 values corresponded to the same model.

4.2. RESULTS

The one-compartment model simulations fitted poorly with the experimental data as they failed to show the stabilisation of plasma phosphate from the early stages of the treatment. In contrast, the two- and three-compartment approaches showed good agreement with the experimental data in both the 4-hour and 8-hour HD. This was seen both graphically and in high R^2 values (0.878 to 0.989). Table 7 presents the most relevant characteristics of the two- and three-compartment model variations providing the best agreement with the experimental data.

Model variation (No.)	Compart-ments	Treatment	k_d (l/min)	k_1 (l/min)	k_2 (l/min)	V_1 (l)	V_2 (l)	V_3 (l)	R^2
3	2	4h	2.8	3.5	-	3	11	-	0.989
4			9	9	-	14	35	-	0.955
5		8h	1	3	-	3	11	-	0.911
6			3.5	9	-	14	35	-	0.878
7	3	4h	2.5	3	5	3	3	8	0.974
8			3.5	5	1	3	11	35	0.979
9		8h	1	3	5	3	3	8	0.911
10			1.4	5	1	3	11	35	0.951

Table 7. The two- and three-compartment model variations providing the best agreement with the experimental data. Model variation numbers correspond to the ones presented in the paper. R^2: Coefficient of determination; k_d: Dialyzer clearance of phosphate; k_1: Mass transfer coefficient 1; k_2: Mass transfer coefficient 2; V_1: Volume of distribution, compartment 1; V_2: Volume of distribution, compartment 2; V_3: Volume of distribution, compartment 3.

The best performance model variations from the 4- and 8-hour treatment were seen as model variation no. 3 (4-h HD) and no.10 (8-h HD), respectively (see Table 7). When the model variations were tested on the opposite treatment (experimental data), the three-compartment model (no. 10) had the best graphical fit and the highest R^2 value (0.979 versus 0.903). Model variation no. 10 corresponded to the best performing model, yielding the highest R^2 value when the evaluation was based on the V values exclusively. Figure 5 illustrates the graphical results of the best performance model variation (no. 10) for the two treatment regimens.

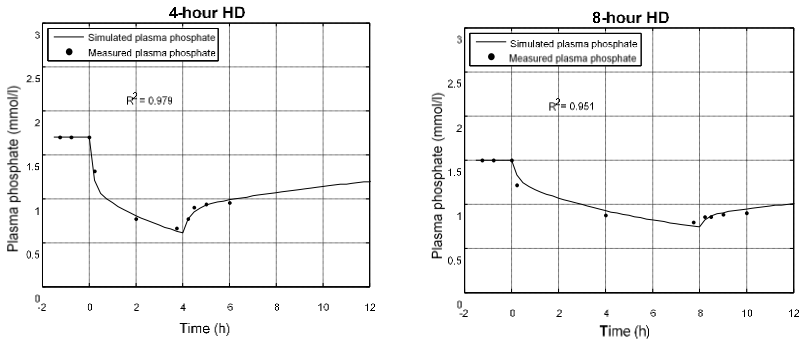

Figure 5. The graphical comparison between the best performance model variation (solid line) and the experimental data (filled circles) for 4-hour HD (left) and 8-hour HD (right). Time = 0 indicates the beginning of HD. R^2: Coefficient of determination; HD: Haemodialysis.

4.3. CONCLUSIONS

In conclusion, both two- and three-compartment model variations provided good agreement with the experimental data and could work as simple tools for prediction

of plasma phosphate in HD patients. However, the three-compartment model performed best. Still, further validation and confirmation is necessary; particularly relevant would be to test the model simulations on other treatment regimens and to include parameters of relevance to the HD patient. It would also be relevant to test other models on the same experimental data to allow comparison between the models.

CHAPTER 5. STUDY II

This chapter summarises the work conducted in the paper entitled "Phosphate kinetic models in hemodialysis: A systematic review" (2). *The summary focuses on the methods, results and conclusions.*

5.1. METHODS

The second study aimed to survey and compare intra- and inter-dialytic phosphate kinetic models in HD to identify their potential and limitations.

A systematic review was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (96). The review also conformed to current review guidelines (97,98). The review included five phases as outlined in Figure 6.

Figure 6. The five phases of the review process.

The preliminary phase included designing a systematic search protocol to structure the search and ensure reproducibility. The main elements of the protocol included reflections on 1) background and research question, 2) inclusion and exclusion criteria, 3) search strategies including selection of information sources/databases, search terms and search functions and 4) strategy for the selection and critical review of the literature. Some key elements of the protocol are presented in Table 8.

Element	Approach
Inclusion and exclusion criteria	Inclusion criteria: 1) records on intra-dialytic and/or inter-dialytic phosphate kinetic modelling within HD therapy, 2) in English, 3) published full-text peer-reviewed journal papers. Exclusion criteria: records with exclusive focus on dialytic phosphate removal, HDF, HF, PD or acute dialysis treatment (not concerning HD).
Information sources/ databases	Primary search channels/databases: PubMed (Medline), EMBASE, Scopus and Web of Science. Additional search databases/information channels: - *Google.com*: Used to identify the most recent material within the area and to stay updated throughout the process. - *Scholar.google.com*: Used to identify scientific literature including specific papers (references from other papers, etc.). - Key scan of relevant references.
Search terms	A variety of different search terms and words relevant to the problem area were applied. This also included synonyms, near synonyms, acronyms and different spellings.
Search functions	Various search functions were used to achieve the most comprehensive search possible: Boolean operators, thesaurus searches, combination of thesaurus and free-text searches, parentheses, truncation, phrase search, abstract, title and keyword search, advanced search, free-text searches, ”Related articles”/”Related citations”, reference searching.

Table 8. Key elements of the search protocol. HD: Haemodialysis; HDF: Haemodiafiltration; HF: Haemofiltration; PD: Peritoneal dialysis.

The preliminary phase led to the search phase. A systematic search was performed in the preselected databases and through the additional search channels using various search terms and functions (see Table 8). The *Search phase* was followed by the *Review and assessment phase*. Relevant records were identified through three steps: 1) removal of duplicates, 2) title and abstract screening and 3) full paper screening. Step 1 – *Removal of duplicates* was performed in RefWorks (2010) using the functions Exact duplicates and Close duplicates. Step 2 - *Title and abstract screening* included an evaluation of language and relevance of subject matter. Step 3 - *Full paper screening* included a thorough scan of each remaining paper to determine its eligibility according to the specific field of interest and the inclusion and exclusion criteria. At this step, papers were excluded if the following exclusion criteria applied: 1) language, 2) wrong intervention/treatment, 3) publication type, 4) unrelated, 5) conference abstracts. The records that were not excluded following these three steps were included in the review.

The next phase, the *Extraction phase*, included extraction of relevant data from each of the included studies according to the following criteria:

- *Model approach*: Author, year, model summary, number of compartments, assumptions, included parameters and comments on strengths and weaknesses.
- *Validation approach - treatment setup*: Dialyzer, dialysis machine, dialysate specifications, dialysate flow rate, blood flow rate, ultrafiltration (total),

dialyzer phosphate clearance and vascular access.

- *Validation approach - study design*: Number of test subjects, gender, age, number of trials, sampling intervals, treatment duration, key findings and validation results (coefficient of determination (R^2) or residual sum of squares (RSS)).

In the final phase, the *Synthesis and reporting phase*, the extracted data were summarised and mapped in the following boxes/tables: 1) Summary of the included models, 2) parameters of the models, 3) treatment setup and 4) study design. The synthesis also included quality assessment of the studies. This included an assessment of each study against 14 quality indicators that were framed according to The Newcastle-Ottawa Scale (NOS)(99). The assessment against each quality indicator provided the individual study with a quality score of 0, 0.5 or 1 (poor, medium or good). The total quality score assigned each study to one of the following categories; low-quality study (0-4), medium-quality study (5-9) or high-quality study (10-14).

5.2. RESULTS

5.2.1. IDENTIFIED STUDIES

A total of 1,964 records were identified from the review after 875 duplicates had been removed. Seventy-six records remained after screening of titles and abstracts, and eleven eligible full-text papers (1,68,88–91,93,94,100–102) were extracted for evaluation and included in the systematic review. However, only nine phosphate kinetic models were identified as three papers reported on the same model (100–102). Table 9 summarises some of the key findings of the eleven studies (1,68,88–91,93,94,100–102).

First author & year	Model structure	Num-ber of para-meters	Evaluation area	Key evaluation results	Total quality score/ Category
Sugisaki 1983 (88)	One-compartment model	3	6h HD	Close agreement with the experimental data but no clear validation results.	2/LQ
Pogglitsch 1989 (90)	Two-compartment model	2	4-5h HD + 12h post-dialysis	Close agreement with the experimental data but no clear validation results.	6.5/MQ
Maasrani 1995(94)	Two-compartment model	11	3h HD + 1h post-dialysis	Close agreement was found: R^2 values between 0.703 and 0.999.	7.5/MQ
Ruggeri 1997 (91)	Two-compartment models	2	4 h HD	All models show satisfying fits with the experimental data. However, one model outperforms the others.	6/MQ
Heaf 1994 (89)	Two-compartment model	4	3-5h HD + 50 min post (and just before the next HD)	No clear validation results.	5/MQ
Heaf 1998 (93)	Two-compartment model	7	3-5h HD + 50 min post (and just before the next HD)	Fits phosphate kinetics poorly.	8/MQ
Spalding 2002 (68)	Four-compartment model	9	4h HD + 1h post-dialysis	Close agreement with the experimental data. How-ever, the validation results are not transparent.	10.5/HQ
Agar 2011 (101)	Pseudo one-compartment model	8	2h and 4h HD + 1h post - dialysis	Close agreement with the experimental data but some minor deviations at the end of HD. The validation results are not transparent	11.0/HQ
Leypoldt 2012 (102)	See Agar et al.	10	-	Unvalidated	4/LQ
Debowska 2015 (100)	See Agar et al.	8	4h HD + 1h post	Close agreement with the experimental data. How-ever, the validation results are not transparent.	11.0/HQ
Laursen 2015 (1)	Two- and three-compartment models	5	4h and 8h HD + 2h post	Fit the experimental data well. A three-compartment model shows the best fit (R^2: 0.979 in the 4-h and 0.951 in 8-h)	9.5/HQ

Table 9. *Key findings of the included studies. HD: Haemodialysis; LQ: Low quality; MQ: Medium quality; HQ: High quality; R^2: Coefficient of determination.*

5.2.2. QUALITY ASSESSMENT

Figure 7 illustrates the extent to which the included studies met the four quality indicator areas; Model approach, Validation and conclusions, Study design and Treatment setup.

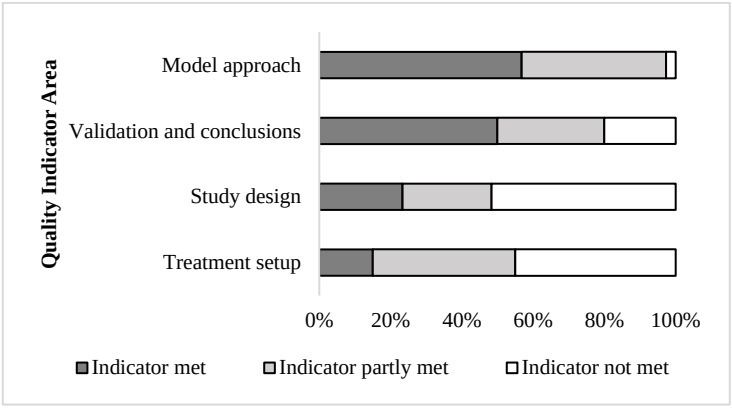

Figure 7. Distribution of the quality of the studies (in percentage) divided by the four quality indicator areas. The four areas are assessed as being met, partly met or not met. Indicators are listed in decreasing order from most frequently met to least frequently met.

Figure 8 shows the extent to which the studies met each of the 14 quality indicators.

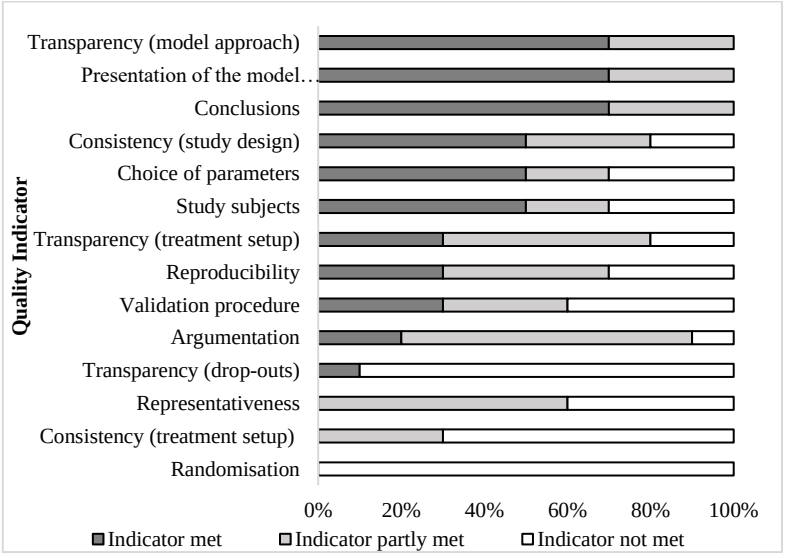

Figure 8. Distribution of the quality score of the studies (in percentage) by quality indicators. The indicators are assessed as being met, partly met or not met. Indicators are listed in decreasing order from most frequently met to least frequently met.

5.3. CONCLUSIONS

Direct comparison of the identified studies was complicated mainly due to variations in model structures and included components. Both one-, two-, three- and four-compartment model structures were identified and 2 to 11 components were identified. Unclear validation results and different evaluation approaches complicated the comparison even further. Hence, the review did not identify a specific model with the best performance. However, it was cautiously concluded that three- and four-compartment models outperform one- and two-compartment models. Moreover, some limitations seem to be present. For instance, it was found that some parameters with known influence on the phosphate kinetics were ignored in the models and could influence model accuracy. Another limitation was a vague determination of model constants and coefficients, which could have been more physiologically based. Hence, the results call for modifications of the current models. Reservations also apply to the evaluation procedures, which are insufficient, especially as far as transparency regarding randomisation, drop-outs and validation results are concerned. Hence, further validation of the phosphate models seems necessary, preferably in identical research settings.

CHAPTER 6. STUDY III

This chapter summarises the work conducted in the paper entitled "Evaluation of a phosphate kinetic model in hemodialysis therapy – assessment of temporal robustness of model predictions". The summary focuses on the methods, results and conclusions.

6.1. METHODS

The third study aimed to modify and validate the most promising phosphate kinetic model from Study I (1), a three-compartment model, to a set of real patient data. The goal was to individualize the model and make it more compatible with physiological expectations. The validation approach aimed at assessing the precision and temporal robustness of the model predictions. This section presents the data set, the modification and the evaluation approaches.

6.1.1. DATA SET

The data set included dialysate and plasma phosphate samples from 12 HD patients. Intra-dialytic samples were collected from each patient during two separate HD sessions. Plasma phosphate and dialysate samples were collected at 30- and 60-minute intervals from the beginning of HD. In addition, post-dialytic plasma phosphate samples covering a 2-hour period were drawn from four of the patients 30 minutes after each dialysis session was terminated.

6.1.2. MODEL MODIFICATION AND VALIDATION

The three-compartment model from study I (1), indicated as model variation no. 8 (4-hour HD) and 10 (8-hour HD), was implemented into Microsoft Office Excel 2013 and modified on the basis of the samples from the 12 HD patients. Modifications were made to the dialyzer phosphate clearance (k_d), the volumes of distribution (V_1, V_2, and V_3), the mass transfer coefficients (k_1 and k_2) and phosphate eliminated through dialysis clearance at time t (*f1*). The dialyzer clearance was assumed to be equal to the individual mean dialyzer clearance calculated from the following equation:

$$k_d = \frac{\frac{(\Sigma \text{ phosphate conc. in dialysate})}{n_d} * \text{mean dialysate flow rate}}{\frac{\Sigma \text{ phosphate conc. in plasma}}{n_p}}$$

The component n_d is the number of individual dialysate samples, and n_p is the number of individual plasma samples. The volumes of distribution in the three compartments were calculated according to the following three equations:

$$V_1 = TBW * 1/3 * 1/4$$

$$V_2 = TBW*1/3 * 3/4$$

$$V_3 = TBW * 2/3$$

Where TBW is total body water calculated from the formulas of P.E. Watson (103).

The samples from dialysis number one (HD1) were used to identify the optimum k_1 and k_2 values in each patient. This included determining the lowest RMSE value using the *Solver* function in Excel.

The R^2 value was determined for the model version with the lowest RMSE value in each individual patient when considering HD1 simulations. Subsequently, the plasma phosphate samples from dialysis number two (HD2) were used to validate the best performance model from HD1 in each patient. The validation on the HD2 values included determination of the R^2 value in each individual patient without changing the model components. Model components were retained to assess the temporal robustness of model predictions.

6.2. RESULTS

Table 10 presents the determined model components (V_1, V_2, V_3, k_d, k_1 and k_2) for each of the 12 patients and the corresponding R^2 values for HD1 and HD2, respectively.

Patient no.	V_1 (l)	V_2 (l)	V_3 (l)	k_d (l/h)	k_1 (l/h)	k_2 (l/h)	R^2 HD1	R^2 HD2
1	2.82	8.46	22.57	10.12	15.89	26.64	0.906	0.984
2*	2.72	8.16	21.75	6.77	11.91	1.78	0.852	0.990**
3*	3.02	9.07	24.19	8.88	7.36	782.50	0.912	0.955
4	3.62	10.85	28.93	9.33	38.50	17.08	0.968	0.983
5*	3.45	10.34	27.57	9.80	11.07	894.15	0.794	0.939
6	2.81	8.44	22.51	9.23	21.50	9.23	0.999	0.992
7	4.36	13.07	34.86	6.63	17.56	21.85	0.931	0.969
8*	3.60	10.79	28.77	8.99	16.55	10.01	0.981	0.971
9	3.87	11.62	30.99	11.26	70.34	14.84	0.987	0.993
10	3.69	11.07	29.51	8.27	29.47	7.30	0.982	0.995
11	2.45	7.35	19.61	6.48	14.46	6.15	0.997	0.995
12	3.69	11.07	29.51	8.72	53.15	6.68	0.997	0.991

Table 10. Model components for each of the 12 patients and the corresponding R^2 values for HD1 and HD2, respectively. The (*) indicates patients who underwent both intra- and post-dialytic sampling. The (**) indicates statistically significant (|z obs. value| > 1.96) difference between R^2 values. R^2: Coefficient of determination; k_d: Dialyzer clearance of phosphate; k_1: Mass transfer coefficient 1; k_2: Mass transfer coefficient 2; V_1: Volume of distribution,

compartment 1; V_2: Volume of distribution, compartment 2; V_3: Volume of distribution, compartment 3.

Figure 9 gives the graphical results of the best performance models (R^2 values) evaluated from HD1 simulations. The median R^2 values were 0.985 and 0.992 for HD1 and HD2, respectively, when fitted to intradialytic samples only. Median R^2 values were 0.882 and 0.963 for HD1 and HD2, respectively, when fitted to both intra- and post-dialytic samples.

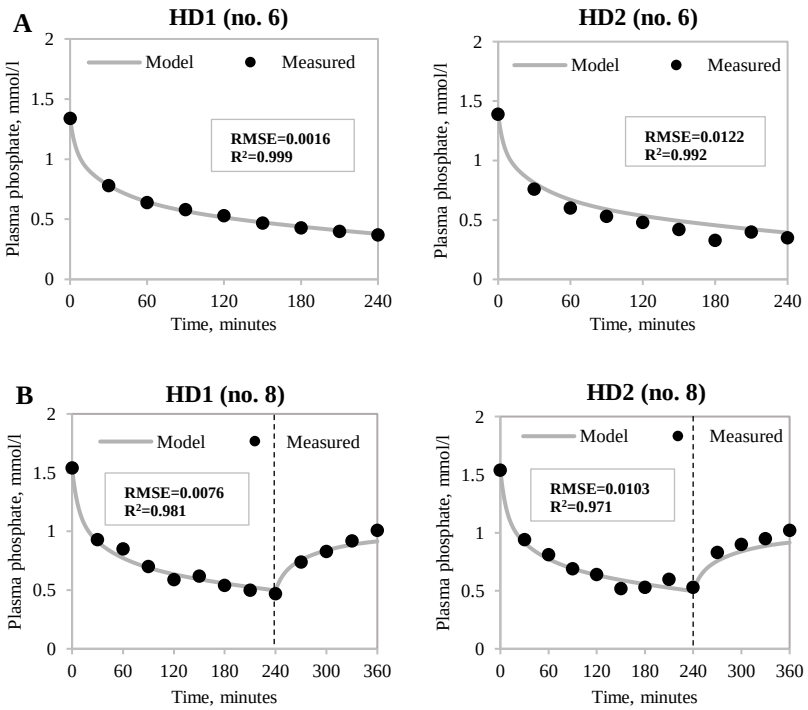

Figure 9. The best performance models on the basis of HD1 R^2 values for intra-dialytic values only (A: patient no. 6) and for both intra-dialytic and post-dialytic values (B: patient no. 8), respectively. The model simulations for HD1 are illustrated on the left, and the model simulations for HD2 are illustrated on the right. The time for termination of dialysis (patient no. 8) is illustrated by the dotted vertical line.

6.3. CONCLUSIONS

In conclusion, the model seems promising regarding simulation of individual plasma phosphate concentrations, especially when considering intra-dialytic phosphate kinetics. Furthermore, the positive results from the HD2 simulations indicate the

temporal robustness of the model predictions. However, even though promising, the model requires further validation on a larger sample, preferably with post-dialytic values to verify the current results and to see if more significant results could be obtained. Moreover, other components potentially influencing the plasma phosphate concentration should be considered.

CHAPTER 7. STUDY IV

This chapter summarises the work conducted in the paper entitled "Implementation of a coagulation component into a phosphate kinetic model in hemodialysis therapy – a potentially useful tool for quantitative detection of clotting problems". The summary focuses on the methods, results and conclusions.

7.1. METHODS

Study IV aimed at adding a coagulation component to the version of the three-compartment model presented in Study III. This section presents the modification and validation approaches.

7.1.1. MODEL MODIFICATION AND VALIDATION

In this study, the three-compartment model was modified and validated on the intra-dialytic dialysate and plasma phosphate samples from the data set (n=12x2) presented in Study III. Modifications were made to the model components *f1*, k_1 and k_2 on HD1 and HD2 samples without changing the other components of the model. The modifications included adding a linear slope as a clearance reduction (/h) to the model to simulate intra-dialytic coagulation of the circuit and dialyzer. This was based on the hypothesis that the dialyzer clearance of phosphate might gradually decrease during treatment due to clotting of the extracorporeal system and dialyzer. Intra-dialytic coagulation is a well-known and unavoidable phenomenon in HD therapy despite anticoagulants. It is known to have a negative effect on treatment effectiveness, for instance, on the dialytic removal of phosphate (72,73,104). The hypothesis that plasma phosphate would decrease following an intra-dialytic linear clearance reduction per hour was an assumption made in this study unsupported by previous studies.

The following two equations are the original (Study I and III) (1) and the modified equations, respectively, for the component *phosphate eliminated through dialysis clearance at time t* (*f1)*:

$$f_1(t) = k_d \times (C_1(t)-C_d(t)) \times s \qquad \text{(original)}$$

$$f_1(t) = k_d \times (C_1(t)-C_d(t)) \times (1-(SL_c \times ((t-t_0)-D_d/2))) \times s \qquad \text{(modified)}$$

In the equations, s indicates dialysis status (0 = no, 1= yes), $C_1(t)$ is the phosphate concentration in plasma (at time t), $C_d(t)$ is the dialysate phosphate concentration (at time t), t_0 is the time for beginning of dialysis, k_d is the mean dialyzer clearance, D_d is dialysis duration and SL_c is the slope of the clearance reduction (/h).

First the Excel *Solver* function was used to identify the two mass transfer coefficients (k_1 and k_2), i.e. the model simulation with the lowest RMSE value, in each of the 24 treatment cases for a model without clearance reduction. Second, the Excel *Solver* function was used to identify the clearance reduction (SL_c) and the two mass transfer coefficients (k_1 and k_2) in each of the 24 treatment cases for a model with clearance reduction. The corresponding R^2 values were calculated.

In addition, the best performance model simulations (with slope) for HD1 and HD2 for each patient were compared with the best performance model without slope for the corresponding treatment.

7.2. RESULTS

Table 11 presents the identified clearance reduction (linear slope) and the corresponding four R^2 values for each of the 12 patients with two treatment cases each. The four R^2 values for each patient represent the agreement between measured and modelled plasma phosphate for the following evaluations; HD1 with and without the slope, and HD2 with and without the slope.

		R^2			R^2	
Patient no.	**Slope (HD1)**	**HD1 without slope**	**HD1 with slope**	**Slope (HD2)**	**HD2 without slope**	**HD2 with slope**
1	0.632	0.906	0.985	0.436	0.965	0.998**
2*	0.000	0.847	0.000	0.000	0.999	0.000
3*	0.280	0.958	0.987	0.115	0.978	0.981
4	0.216	0.968	0.986	0.161	0.990	0.999
5*	0.310	0.820	0.870	0.201	0.983	0.998**
6	0.000	0.999	0.000	0.011	0.994	0.994
7	0.395	0.931	0.993**	0.221	0.976	0.991
8*	0.000	0.992	0.000	0.127	0.983	0.988
9	0.000	0.987	0.000	0.180	0.996	0.999
10	0.156	0.982	0.989	0.128	0.994	0.997
11	0.057	0.997	0.998	0.000	0.998	0.000
12	0.079	0.997	0.999	0.000	0.993	0.000

Table 11. Identified slope and the corresponding R^2 values (HD1 with and without slope plus HD2 with and without slope) for each of the 12 patients. The (*) is patients who underwent both intra- and post-dialytic sampling. The (**) indicates statistically significant (|z obs. value| > 1.96) difference between the R^2 values (without and with slope) for the specific treatment.

Figure 10 gives an example of the graphical results for a typical treatment, patient no. 5 HD1, i.e. the treatment with the ninth largest relative improvement in RMSE (median relative improvement).

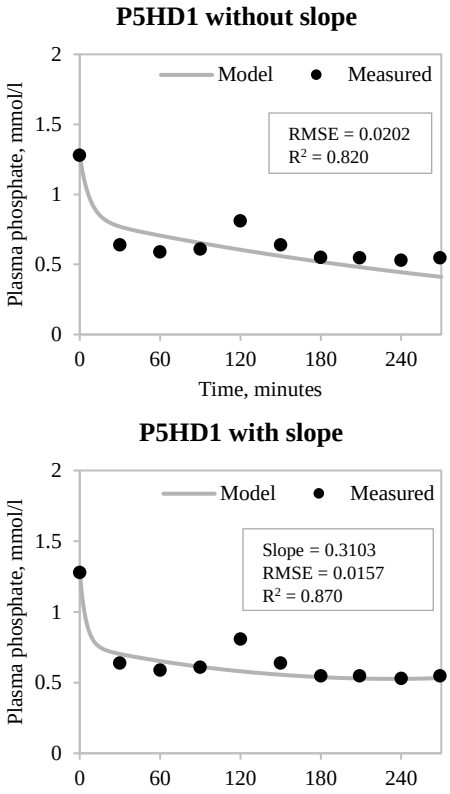

Figure 10. The graphical comparison between the model (solid line) and experimental data (filled circles) for a typical treatment (patient no. 5 HD1) without and with a linear slope.

7.3. CONCLUSIONS

It can cautiously be concluded that a linear clearance reduction is promising in phosphate kinetic modelling. The linear clearance reduction may be explained by intra-dialytic coagulation. However, making any final conclusions about the completeness, usefulness and validity of the model is not possible until further testing of the model has been accomplished. Future studies could benefit from more patients and more samples in each patient case. Such studies should address potential risk factors for intra-dialytic clotting of the extracorporeal system and dialyzer. Further development of the model may produce a useful tool with a potential for quantitative detection of intra-dialytic clotting problems.

CHAPTER 8. DISCUSSION

This chapter is divided into five subsections: 1) Summary of the main findings, 2) Interpretation of the main findings and modelling approaches, 3) Methodological considerations, 4) Conclusions and 5) Future perspectives.

8.1. SUMMARY OF MAIN FINDINGS

This PhD study on hyperphosphataemia management in HD therapy presents some new approaches within the field of phosphate kinetic modelling in HD therapy. Four studies were conducted.

Study I involved developing and evaluating new phosphate kinetic modelling approaches based on distribution volume assessment. One-, two- and three-compartment structures were tested on experimental data from eight HD patients at 4 and 8 hours of HD and 2 hours after dialysis. The two- and three-compartment approaches showed good agreement with the experimental data (average plasma phosphate samples). A three-compartment approach had the best fit. The identified model components and coefficients for the three-compartment model were: V_1=3 l, V_2=11 l, V_3=35 l, k_1=5 l/min and k_2=1 l/min. The most suitable dialyzer phosphate clearance (k_d) differed between the 4-hour and 8-hour treatments (3.5 l/min versus 1.4 l/min).

Study II, a systematic review of existing phosphate-kinetic models in HD therapy, identified 11 relevant studies examining nine different models. The papers were thoroughly reviewed, compared and assessed. It was not possible to single out any particular best-performing model due, among others, to lack of validation results.

In Study III, the best performance model from Study I, a three-compartment model, was tested on individual patient data (n=12) including dialysate and plasma phosphate samples from two separate treatments from each patient. The model was modified with the aim of individualising the model and making it more compatible with physiological expectations. When fitting the model to individual plasma phosphate samples, we found a rather good agreement with the model simulations in most patient cases, especially for intra-dialytic values, indicating a high empirical validity. Temporal robustness was found when the model from HD1 was tested on HD2 samples; eight of the 12 patients demonstrated higher R^2 values for HD2 than for HD1 – this included three patients with both intra- and post-dialytic samples. The median (interquartile range) model coefficients and components were: V_1=3.53 (2.82-3.69) l; V_2=10.57 (8.46-11.07) l; V_3=28.17 (22.56-29.51) l; k_d=8.94 (7.90-9.45) l/h, k_1=17.06 (13.82-31.73) l/h; k_2=12.43 (7.15-23.05) l/h.

The model in Study IV presented a build-on to the model presented in Study III. The modifications included adding a linear clearance reduction (/h) as an assumed

coagulation component to the model. The model with the coagulation component was validated on the patient data presented in Study III (24 treatments). Seventeen of the 24 model simulations improved when the linear clearance reduction was added to the model. However, only three of the 17 improvements in R_2 values were found to be statistically significant (|observed z value|>1.96). The identified (median) components and coefficients for the model in Study IV were (n=24): slope=0.125/h; V_1=3.53 l; V_2=10.57 l; V_3=28.17 l; k_d=8.88 l/h, k_1=44.89 l/h; and k_2=8.76 l/h. We found a correlation between the slopes for HD1 and HD2 for a given patient. No correlation was found between the slopes and the corresponding 3-hour-point plasma phosphate concentrations.

8.2. INTERPRETATION OF THE MAIN FINDINGS AND MODELLING APPROACHES

8.2.1. MODEL COMPONENTS AND COEFFICIENTS

The difference in k_d values in Study I (1) between the 4- and 8-hour model simulations (3.5 l/min versus 1.4 l/min) for the most promising model, the three-compartment model, was expected due to different diffusive rates considering the duration of dialysis (66). The identified volumes of distribution values (V_1=3 l, V_2=11 l and V_3=35 l,) were to some extent compatible with physiological expectations. The total volume of distribution of phosphate (49 l) would be consistent with the TBW in an average person weighing approximately 70 kg (103) and it would be consistent with the speculation that phosphate has a large distribution volume (69). Furthermore, the distribution volumes in compartment 1 (V_1=3 l) and 2 (V_2=11 l) approximately correspond to the fluid in the plasma and in the interstitial space, respectively (105). However, a limitation of the distribution volume assessment approach in Study I is that components such as gender, age, weight and height were not considered, even though they are known to influence the TBW (103). The k_1 and k_2 values (k_1=5 l/min and k_2=1 l/min) were evaluated as likely, considering biological processes, though difficult to assess. The k_d values were questionable, however, as they were extremely high and thus unlikely considering current treatment regimens (66).

The components and coefficients of the model presented in Study I (1) were adjusted in Study III (and Study IV) on the basis of model modification on individual patient data. These adjustments enabled individualisation of the model and thus produced a higher theoretical validity; the volumes of distribution (median : V_1=3.53 l; V_2=10.57 l; V_3=28.17 l) were identified using acknowledged formulas (103) that took into account gender, age, weight and height, and the dialyzer phosphate clearance (median: k_d=8.94 l/h) was calculated from phosphate samples (plasma and dialysate) and observed dialysate rates in the specific patient case. However, the approach of determining the mass transfer coefficients (median: k_1=17.06 l/h; k_2=12.43 l/h) using the *Solver* function in Excel generated some rather extreme and thus physiologically

unlikely values in a few treatment cases. This problem was especially pronounced in a couple of the treatment cases with both intra- and post-dialytic samples – a result that might indicate that further model modifications are required for this particular type of data. The problem with extreme k_1 and k_2 values was also observed in some of the treatment cases in Study IV.

The assumption about constant compartment volumes not accounting for individual fluid removal during HD is a questionable element of the model approaches in Study I, III and IV. Hence, ultrafiltration is known to affect the dialysis clearance of phosphate (64,81). Another questionable assumption in Study I and III is that dialysis removal and diffusion between compartments were considered the only effects causing changes in plasma phosphate. This implies that we did not take into consideration different variations in the treatment such as dialysate rate, dialyzer type and blood flow rate – factors that could all potentially influence the phosphate level. The model approach also ignores other influencing factors such as hormonal influence, intra-dialytic clotting of the extracorporeal system and dialyzer, calcium concentration, pH level, phosphate-binding agents, intestinal absorption and skeletal turnover (64,72,73,86,104). Ignoring these potential influencing factors is also a problem in Study IV. However, in this study, a coagulation component was added as a linear clearance reduction to the model in an attempt to simulate the intra-dialytic clotting of the extracorporeal system and dialyzer. The linear clearance reduction led to improvements (R^2) in 17 of 24 model simulations, indicating that the input of a linear clearance reduction could be a valid component in intradialytic phosphate kinetic modelling in HD therapy. However, only three of the 17 improved R^2 results obtained after adding the clearance reduction to the model were considered statistically significant - a result that might be caused by the relatively limited number of samples in each treatment. Hence, more frequent sampling should be considered in future studies. In the study, it was concluded that the effect of the linear clearance reduction may be explained, at least partly, by the intradialytic coagulation. However, this conclusion was made on a rather uncertain basis and further validation is required before definitive conclusions can be made. Even so, the input of the clearance reduction seems to improve the model and is considered a promising modelling approach.

Ignoring potentially influencing treatment-specific and patient-specific factors on plasma phosphate concentration is a general problem within phosphate kinetics modelling. This is evident from the systematic review (2). In the review, it was found that existing models include between two and eleven model components with known influence on the phosphate balance. However, none of the models were found to consider all potentially influencing factors – a perspective that could affect the accuracy of the models in some patient cases. Moreover, ignoring these factors questions the theoretical validity of existing models and limits their practical potential.

8.2.2. MODIFICATION AND VALIDATION APPROACHES

The modification and validation approach in Study I is advantageous to some extent. One advantage is that the model is modified and tested on two different treatment regimens; 4- and 8-hour HD (95). The promising results of both 4-hour HD and 8-hour HD increase the prospect that the model will be used as it may be useful in both CHD and NHD patients (13). Another advantage is the additional modification and validation on 2-hour post-dialytic phosphate concentrations (95). In comparison to the normal 1-hour post-dialytic approach, the 2-hour post-dialytic modifications and testing is improvement on the approaches in previous studies (2). Although the modification and validation approach is advantageous in these respects, some important limitations should be acknowledged concerning the modification and validation approach in Study I. One important issue is that the model simulations are modified and tested on experimental data (95) that include mean plasma phosphate values exclusively. This could produce incorrect results in some individual patients. For instance, the total distribution volume is known to differ according to gender, age, weight and height (103). Another issue is the sample size; the modifications and testing on mean values based on patient values from only eight HD patients necessarily means that our results should be confirmed in a larger population.

Some of the modification and validation problems in Study I (1) are addressed in Study III (and IV). One important improvement in Study III (and IV) in comparison to Study I is the modifications and validation on individual patient data. The individualised approach is highly relevant as patient- and treatment-specific factors are known to influence the plasma phosphate concentration (64,72,73,86,104). Thus, in Study III (and IV), the component k_d was determined on the basis of patient-specific treatment values (dialysate flow rate) and collected dialysate and blood samples. This produced values more in line with expected clearance values reported in previous studies (68,85,106). In comparison, the dialyzer clearance component was determined by system model simulations (Excel) in Study I. In addition to improvements of the dialyzer clearance component, individualisation of the volumes of distribution components (V_1, V_2 and V_3) was also incorporated into the model (Study III and IV). Hence, the components included individualised calculations of TBW by taking into account the individual patient's weight, age, gender and height. Overall, these changes have heightened the theoretical validity of the model compared to the model presented in Study I (16). Another improvement in Study III (and IV) in comparison to Study I is the larger sample size of 12 HD patients; even so, the sample size is still considered relatively small, especially the proportion of patients (4 of 12 patients) with post-dialytic values. Despite the relatively small sample size, the validation of the model on two sets of individual patient data in each patient case (HD1 and HD2) strengthens the credibility of the validation results. Furthermore, as illustrated in Study III, this approach enables assessment of the temporal robustness of the model predictions. In this regard, a rather high agreement was found when comparing the model simulations to HD2 samples, even though the model was only modified to HD1 samples. This is assessed to indicate the temporal robustness of the model. However, it is expected that

treatment-specific factors will deviate, for instance dialyzer phosphate clearance, especially if the model is validated on treatments separated by longer intervals than in the present study. The validation on data sets from two separate treatments to test for temporal robustness of model predictions has not been performed in previous studies and thus constitutes an untested validation approach within phosphate kinetics modelling (2).

From the results of the systematic review (2), it is evident that eight models (1,68,88,90,91,94,100,101), including the model presented in Study I (1), are promising in terms of accuracy, i.e. they provide high agreement with experimental data (2). However, the validation approaches seem to be encumbered with different challenges that question their validity. The main problems are that validation is based on small datasets, which could compromise generalisability; and lack of clear validation results (2), which compromises the quality and accuracy of the models. Moreover, consistency regarding study designs and treatment setups is lacking, and evaluation of dropouts and randomisation is not sufficiently described (2).

8.2.3. MODEL STRUCTURE AND COMPLEXITY

One of the main results in Study I (1) was the need for more than one compartment to simulate the measured plasma phosphate. This result confirms the results of other model studies examined in the systematic review (2). The studies in the systematic review include between two and four compartments (68,89–91,93,94) or demonstrate a one-compartment model structure with an influx from an unknown compartment (88,100–102) – an approach that can be interpreted as identical to a two-compartment model. The result that a simple one-compartment model is considered insufficient to describe intra- and post-dialytic phosphate kinetics was expected since the plasma phosphate is known to stabilise from early in the treatment, indicating an influx of phosphate from another compartment (107–109). The stabilisation of phosphate is evident from the validation results in Study I, III and IV.

In Study I, we found a good agreement with the experimental data with both the two- and the three-compartment model approaches, even if the best performance model had a three-compartment structure. This result is in accordance with three (68,93,94) of the studies identified from the review which found it difficult to describe the phosphate stabilisation using a two-compartment approach. The model by Spalding et al. (68) even found it difficult to describe the dialytic phosphate kinetics using a three-compartment model in some patient cases. This result might testify to the need for individualising the model structure in future modelling. The need for a multi-compartment model to simulate phosphate kinetics confirms the complexity of phosphate kinetics (54,81).

In Study III and IV, the three compartments are set to be consistent with plasma (compartment 1), the interstitial space (compartment 2) and the intra-cellular space

(compartment 3). This approach is similar to the common assumption in the two-compartment approaches that one compartment is equal to the extracellular space and another is equal to the intracellular space (2). This approach, however, does not allow for the possibility of other distribution volumes. The model approach presented in Study I (1) deviates slightly in this respect because it is based on distribution volume assessment and therefore includes specific suggestions, in litres, for distribution volumes for the included compartments. However, the identified volumes of distribution (V_1=3 l, V_2=11 l and V_3=35 l) of the best performance model in Study I take approximately the same form as expected for plasma, the interstitial space and intra-cellular space and thereby follow the pattern of other studies. The volumes of distribution (V_1=3 l, V_2=3 l and V_3=8 l) of the second best performance, the three-compartment model in Study I (see Table 7), indicate that phosphate is only distributed in the extracellular space. This result would not be consistent with the current speculation that phosphate is a small molecule with a large distribution volume (69).

Although the results indicate the need for a minimum of two compartments, in the end the choice of the number of compartments would often depend on the ability of the individual model to simulate the experimental data. Hence, a one-compartment simulation like the models proposed by Sugisaki et al. (88) and Agar et al. (101) with an in-flow of phosphate from an unidentified depository could prove just as useful as a multi-compartment model like the one proposed by Spalding et al. (68) if it more accurately fits the experimental data (68). In the end, the usefulness of the model will sometimes depend on the strength of its empirical validity albeit this could compromise its theoretical validity (16). It is considered that a model with high empirical validity could be a useful tool in the prediction of plasma phosphate kinetics and phosphate removal even though the theoretical validity was compromised. However, if the theoretical validity is compromised, this would limit the usefulness of the model if it is to be used to increase our understanding of biological processes and treatment effects. Overall, the usefulness of the model will be determined by its intended purpose (16).

8.2.4. MODEL POTENTIAL

Study I (1) provides a novel, yet immature model approach with distribution volume assessment as a seemingly new feature within the modelling field. Despite some questionable assumptions and coefficients, the model could have the potential to predict plasma phosphate values and be applied in practice. This is stated on the basis of the high empirical validity considering both 4- and 8-hour (plus 2-hour post-dialysis) model simulations. In this regard, however, it should be considered that the model has been modified and tested on experimental data (95) that include mean plasma phosphate values exclusively. This could produce incorrect results in some individual patients, since different treatment- and patient-specific factors could influence the phosphate concentration (64,73,86). The approach of distribution volume assessment to determine distribution volumes in phosphate kinetics modelling

could, however, be a rather interesting method in future model studies. The feasibility of this approach should, however, be evaluated in individual experimental data.

The promising results of Study III indicate that the three-compartment model could serve as a tool for prediction of individual plasma phosphate kinetics. It also has the potential for quantifying dialytic phosphate removal based on prediction from the treatment-specific pre-dialytic phosphate sample. However, even though improved and less descriptive, the model still has some questionable features. For instance, the mass transfer coefficients (k_1 and k_2) are questionable in a few cases and the model continues to ignore other potentially relevant factors that influence the plasma phosphate level (64,73,86). Hence, these issues question the theoretical validity of the model and it may therefore benefit from further modifications in future studies.

When considering the promising results from the model validations in Study IV, it seems that a linear clearance reduction could be beneficial in intra-dialytic phosphate kinetic modelling in HD therapy. However, of the 17 treatments favouring a linear clearance reduction, only three showed statistically significant improvements. Further validation should thus be made to make any final conclusions about the model input of a linear clearance reduction. Intra-dialytic coagulation is considered to be a reasonable or at least partial explanation for the clearance reduction in the model. Hence, intra-dialytic coagulation of the extracorporeal system and dialyzer is an unavoidably phenomenon in HD therapy and is known to have a negative effect on phosphate removal (72,73). Adding a linear clearance reduction to the model is a novel approach within the field of phosphate kinetics modelling and could perhaps be beneficial in future modelling. For instance, it is suggested that it could be applied as a tool for quantitative detection of individual clotting problems.

Other models with practical potential include the models by Agar et al. (101) and Spalding et al. (68). These models were found to be high-quality models (2) that showed promising validation results. However, no clear validation results were provided to verify the promising results. Still, it appears that the experimental stage of the model by Agar et al. (101) is most advanced. Another potentially useful model is that by Maasrani et al. (94). This model has the largest number of model components (n=11) and shows good agreement with experimental data. However, the validation results of this model are questionable as the model has been tested only in four paediatric patients. Overall, it is difficult to conclude which model performance is best based on existing validation results. A direct comparison of the models and their performance is also hampered by differences in treatment setups and sampling methods. For example, using blood flow rate and dialysate flow rate together with dialyzer membrane and surface area may affect phosphate clearance (72). It should also be considered that some models may be limited to specific treatment modalities. Hence, it is recognized that short 2-h HD (SHD), NHD and CHD differ in terms of solute removal, time and blood flow rates (66,71,110,111). Only the model variations presented in this thesis and the model by Agar et al. (101) have been tested in different treatment regimens. Moreover, it should be stated that the models by Ruggeri et al.

(91) and Sugisaki et al. (88) do not simulate post-dialytic phosphate kinetics – a perspective that limits their use.

Finally, when appraising the potential of a model, its complexity also has to be considered. On the one hand, a simple approach such as the model by Agar et al. (101) would be relevant because of its practical potential. On the other hand, a more sophisticated model like that proposed by Spalding et al. (68) may increase our understanding of the biological processes (16,17). In the end, which model is the better would depend, as already stated, on the field of application.

8.3. METHODOLOGICAL CONSIDERATIONS

8.3.1. STUDY I

The modification and validation based on mean experimental values and the ensuing lack of individualisation of model components and coefficients is a major weakness of this study. This is especially evident from the high k_d values, which are not likely considering current treatment regimens (66). Ignoring of age, gender, height and weight in the calculation of the volumes of distribution is another important issue. These shortcomings question the theoretical validity and thus the potential of the model. Another issue is the small sample size (n=8).

Leaving aside the major methodological issues, the modification and validation approach is advantageous to some extent as the model is modified and tested on two treatment regimens (4- and 8-hour HD) and on a 2-hour post-dialysis basis. Furthermore, it is evident that some of the two- and three-compartment model simulations show high empirical validity. Hence, although it is at a preliminary stage, the model approach must be considered promising and it does provide indications of the best model simulation. However, further validation and confirmation in larger datasets with individual data is required.

8.3.2. STUDY II

The review thoroughly evaluated and compared existing phosphate kinetic models and related validation approaches. Moreover, it followed acknowledged guidelines within the field of systematic reviewing (91–93). However, some of the methodological approaches need to be considered, for example the assessment approach, i.e. the evaluation of the model studies against the 14 quality indicators. Firstly, these indicators comply only with a modified version of the acknowledged guidelines, the NOS scoring system (99). This could question the validity of the assessment scale. However, as no other specific assessment tool is currently available, using the modified version of the NOS score was considered the most appropriate alternative. Secondly, the use of the 14 quality indicators risks making the assessment too subjective. All authors were involved in the *Review and assessment phase* to reduce the risk of subjectivity. Thirdly, we cannot ignore the possibility of inconsistency between what was reported in the individual study and what was

actually done. Such discrepancies could result in an underestimation or overestimation of the quality of the study reviewed. Yet, the applied assessment approach is considered valid as the reader have to base any assessment on the study report alone.

The search for relevant literature included a comprehensive search in four databases and additional hand searches, for instance, scans of key reference lists, in order to ensure that the search was exhaustive. However, we assume that all relevant literature may not have been included in the review as the inclusion and exclusion criteria stipulated that the review was limited to full-text papers in English. Another methodological consideration is the exclusive focus on phosphate modelling in HD therapy. This focus implies that the review does not consider potential HDF models. These models could have been included in the review. However, this would have complicated comparison of the models as the phosphate kinetics during HD and HDF differ (67,112).

8.3.3. STUDY III

An important advantage of this study is that individual experimental data were used to modify and validate the model. Furthermore, the volumes of distribution (V_1, V_2 and V_3) and the dialyzer phosphate clearance (k_d) were adjusted on the basis of values from the individual patient. These modifications heighten the individualisation of the model and its theoretical validity. However, it is evident that a few mass transfer coefficients (k_1 and k_2) are rather extreme, and thus unlikely, especially when looking at the treatment cases with both intra- and post-dialytic samples. Hence, the model might benefit from further model modifications for this particular type of data.

The validation on two data sets (HD1 and HD2) in each patient case is another strength of this study. In this context, the promising model simulations obtained from the validation on HD2 values indicate the temporal robustness of the model. However, in this regard, it should be stated that the promising HD2 model simulations could be a result of the relatively closely spaced sampling interval - HD1 and HD2 samples were collected only a week apart. Moreover, the consideration of 2-hour individual post-dialysis kinetics separate the model study from previous studies as the typical approach has been to consider 1-hour post-dialysis kinetics (2).

Although promising model results were obtained, it should be mentioned that the results are limited to a relative small sample (n=12). Hence, further validation and confirmation in larger datasets are required especially to evaluate the post-dialytic model simulations since only four patients agreed to stay for post-dialytic sampling. However, although the results rely on a small dataset, we consider the model promising, especially in the simulation of individual intra-dialytic plasma phosphate levels. It should also be noted that the sample size is comparable to that of many other model studies (2).

8.3.4. STUDY IV

The modelling and validation approaches are relatively similar in Study III and IV. Hence, some of the methodology elements from Study III (section 8.3.3.) recur in Study IV. The experimental data are derived from the same treatments (although only intra-dialytic values are used in Study IV), and the V_1, V_2, V_3 and k_d values are calculated in the same way in the two studies (and thus identical for the eight patients with only intra-dialytic data). In Study III, the k_1 and k_2 values were determined using the *Solver* function in Excel which led to a couple of rather extreme values. Like in Study III, Study IV also produced some rather unlikely k_1 and k_2 values in some of the treatment cases. These relatively extreme k_1 and k_2 values may be related to the relatively high number of variables estimated in the model (one slope and two mass transfer coefficients) relative to the number of data points in a given treatment leading to an overfit of model simulations to unexplained data variations.

Adding the linear clearance reduction as a linear slope seems to improve the model as 17 of the 24 model simulations showed a better fit. This approach has not been tested prior to this study and could be a promising feature in phosphate kinetic modelling in HD therapy. However, the few statistically significant results (three of the 17 R^2 values) call for further evaluation. Future studies can perhaps benefit from more frequent sampling.

As stated in the paper, intra-dialytic coagulation could likely explain, at least partly, the linear clearance reduction. However, the so-called ‘mobilization’ could also be explained by other factors. For instance, it has been proposed that an intrinsic phosphate target concentration could trigger an inflow of phosphate from an unknown compartment (68,88,90). However, the result that no correlation was found between the slopes (n=24) and the corresponding plasma phosphate concentrations at the 3-hour time point speaks against this argumentation. To make any final conclusions about the reason for the promising results when adding the clearance reduction to the model is, however, not possible on the basis of the results of Study IV - further studies in a more controlled setup would therefore be necessary to evaluate the assumption of an intra-dialytic coagulation component.

8.4. CONCLUSIONS

In conclusion, this PhD thesis presents novel perspectives and ideas that may inform the work to devise clinically useful solutions to improve hyperphosphataemia management in HD therapy. Regarding the overall research hypothesis of the thesis, it may be concluded that a three-compartment model can simulate phosphate kinetics in haemodialysis with a strong correlation between simulations and patient specific data.

From the systematic review, it can be concluded that no phosphate kinetic model seems to be ready to be implemented, even though some models have shown promising results. Lack of clear validation results, ignorance of factors that may influence plasma phosphate and questionable physiological assumptions are some of

the challenges complicating the use of existing models. Moreover, differences between evaluation procedures hamper direct comparisons between models – a perspective that prevents us from determining which model performs best. However, it can be cautiously concluded that one- and two-compartment model simulations do not sufficiently simulate phosphate kinetics.

The three-compartment model (Study I, III and IV) is considered promising, especially the versions presented in Study III and IV. These model approaches showed promising results when fitted to individual patient data and demonstrated temporal robustness. Hence, these model approaches seem to have the potential to simulate individual intra- and post-dialytic (2 hours) phosphate kinetics and could potentially work as a quantification tool to determine treatment-specific dialytic phosphate removal if the pre-dialytic phosphate concentration is provided. Furthermore, adding a linear clearance reduction seems to be a promising feature and to be a relevant approach in future modelling studies. However, it remains speculative whether the clearance reduction could be explained, or partly explained, by intra-dialytic coagulation in the extracorporeal system and dialyzer. The overall conclusion is, therefore, to recommend further refinement and validation of the model in a larger sample before considering it for practical use. Moreover, it could be of relevance to consider other factors that potentially influence the phosphate concentration to increase the theoretical validity of the model.

8.5. FUTURE PERSPECTIVES

As stated in the Conclusion, further refinements and validation are needed before the three-compartment model can be considered for practical use. First of all, it would be relevant to test the model on a larger dataset including both intra- and post-dialytic samples from individual HD patients. Such a study could provide more reliable and thus more useful validation results. It would also be expedient to include into the model other relevant model components potentially affecting plasma phosphate levels in individuals.

The suggestion to add a linear clearance reduction to the model should also be further investigated. First, it would be relevant to test its potential in a larger sample. Second, if possible, it would be relevant to investigate further if the linear clearance reduction can really be explained by intra-dialytic clotting or if another explanation could be found.

Furthermore, it would relevant to test the model simulations from Study III and IV on prolonged HD. Hence, promising validation results for 8-hour HD have already been demonstrated in Study I.

Finally, it should be stated that future research should be conducted to further explore the phosphate kinetics models in general. For instance, in future research, it would be relevant to investigate all phosphate kinetic models in identical research settings but with different treatment modalities. Such a comparable research set-up could help determine if a particular model would be more suitable in a certain setting than in others. Furthermore, such comparable research could help identify the best model

performance. An updated literature search should be performed on beforehand to ensure that all relevant phosphate kinetic models are included.

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